AstraZeneca

What science can do

AstraZeneca Annual Report and Form 20-F Information 2018

Welcome

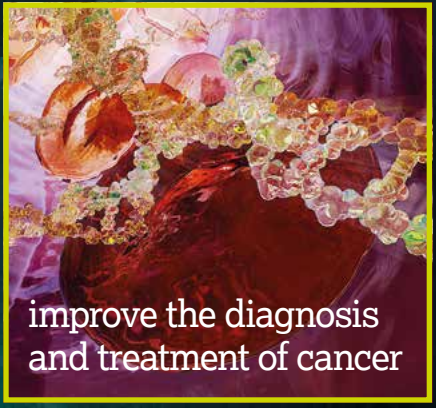
We are a global, science-led pharmaceutical business, and in this Annual Report we report on the progress we made in 2018 in pushing the boundaries of science to deliver life-changing medicines and demonstrating what science can do.

Science *can* deliver value to patients, payers and society

Innovative Value Strategies and indication-based pricing
See page 17

deliver complete disease management in China

Innovative ideas in healthcare
See page 37



improve the diagnosis and treatment of cancer

Pioneering the use of circulating tumour DNA
See page 28

Searching for new treatment options
See page 49

help find a cure for ovarian cancer

help people undergoing heart bypass surgery

New ways of treating heart disease
See page 61

Use of terms
In this Annual Report, unless the context otherwise requires, 'AstraZeneca', 'the Group', 'we', 'us' and 'our' refer to AstraZeneca PLC and its consolidated entities.

Front cover image: Circulating tumour DNA
AstraZeneca has pioneered the use of circulating tumour DNA (ctDNA) in the diagnosis of cancer. Pieces of DNA break off from a tumour and circulate in the bloodstream where they can be analysed to give genetic information about a patient's tumour. This allows healthcare professionals to determine the right treatment for the patient using a minimally invasive blood test.

Contents

Financial highlights

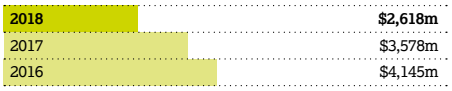
Total Revenue*

Down 2% to $22,090 million at actual rate of exchange (down 2% at CER), comprising Product Sales of $21,049 million (up 4%; 4% at CER) and Externalisation Revenue of $1,041 million (down 55%; 55% at CER)

$22.1bn

Net cash flow from operating activities

Down 27% at actual rate of exchange to $2,618 million



$2.6bn

Reported operating profit

Down 8% at actual rate of exchange to $3,387 million (down 7% at CER)

$3.4bn

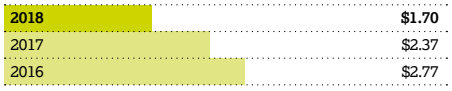
Core operating profit

Down 17% at actual rate of exchange to $5,672 million (down 17% at CER)

$5.7bn

Reported EPS

Down 28% at actual rate of exchange to $1.70 (down 29% at CER)



$1.70

Core EPS

Down 19% at actual rate of exchange to $3.46 (down 19% at CER)

$3.46

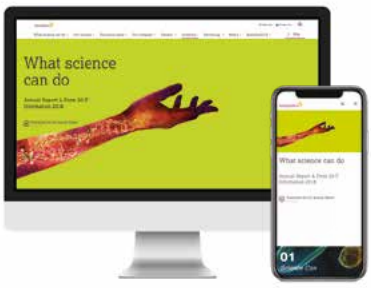
// Denotes a scale break. Throughout this Annual Report, all bar chart scales start from zero. We use a scale break where charts of a different magnitude, but the same unit of measurement, are presented alongside each other.

For more information in relation to the inclusion of Reported performance, Core financial measures and constant exchange rate (CER) growth rates as used in this Annual Report, see the Financial Review from page 74.

* As detailed on page 154, Total Revenue consists of Product Sales and Externalisation Revenue.

For more information within this Annual Report

For more information, see www.astrazeneca.com



This Annual Report is also available on our website, www.astrazeneca.com/annualreport2018

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AstraZeneca at a glance

A global science-led business delivering medicines to patients through innovative science and excellence in development and commercialisation.

Our Purpose is to push the boundaries of science to deliver life-changing medicines. We want to be valued and trusted by our stakeholders as a source of great medicines over the long term.

Our strategic priorities

Reflect how we are working to achieve our Purpose

1. Achieve Scientific Leadership
2. Return to Growth
3. Be a Great Place to Work

A science-led innovation strategy

Strategy from page 18 and Key Performance Indicators from page 20.

Distinctive R&D capabilities:
Small molecules, oligonucleotides and other emerging drug platforms, as well as biologic medicines, including immunotherapies, and innovative delivery devices

8
new molecular entities (NMEs) in Phase III/ pivotal Phase II or under regulatory review, covering 15 indications

Broad R&D platform in three main areas

Achieve Scientific Leadership from page 25 and Therapy Area Review from page 50.

Oncology
Our ambition is to push the boundaries of science to change the practice of medicine, transform the lives of patients living with cancer, and ultimately eliminate cancer as a cause of death

Cardiovascular, Renal and Metabolism
As science uncovers commonalities between cardiovascular, renal and metabolic diseases and their associated complications, we aim to transform how they are understood and treated

Respiratory
Our research focuses on the underlying causes of respiratory diseases, using new modalities to pursue previously hard-to-reach targets, with the ambition of achieving remission or even cures for patients

Other Disease Areas
We are also selectively active in the areas of autoimmunity, neuroscience and infection

Portfolio of specialty and primary care products (Product Sales)

$6,028m
29% of total
2017: $4,024m
2016: $3,383m

Sales growth of 50% (49% at CER), including:

Imfinzi sales of $633 million, reflecting ongoing launches

Lynparza sales of $647 million, representing growth of 118% (116% at CER), driven by expanded use in the treatment of ovarian cancer and first approvals for breast cancer

Tagrisso sales of $1,860 million, representing growth of 95% (93% at CER)

$6,710m
32% of total
2017: $7,266m
2016: $8,116m

Sales decline of 8% (8% at CER), including:

Crestor sales of $1,433 million, down 39% (40% at CER) reflecting generic competition

Brilinta sales of $1,321 million, representing growth of 22% (21% at CER), due to continued market penetration

Farxiga sales of $1,391 million, with growth of 30% (30% at CER), including a sales increase of 45% in Emerging Markets (52% at CER) to $336 million

$4,911m
23% of total
2017: $4,706m
2016: $4,753m

Sales growth of 4% in the year (3% at CER), including:

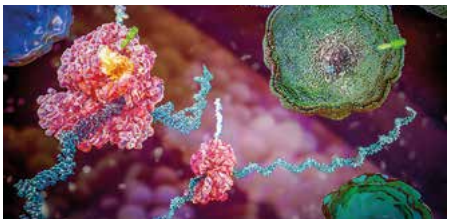
Fasenra sales of $297 million, performing exceptionally well in the countries where it was launched

Pulmicort sales growth of 9% (8% at CER) to $1,286 million

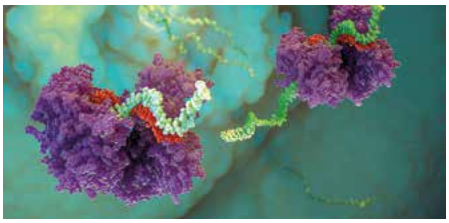
Symbicort sales decline of 9% (10% at CER) to $2,561 million, as competitive price pressures in the US continued

$3,400m
16% of total
2017: $4,156m
2016: $5,067m

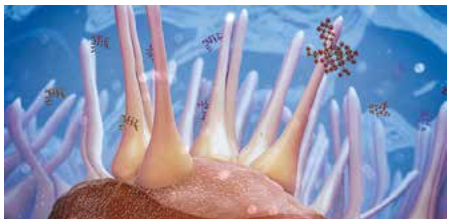
Product Sales declined by 18% (19% at CER) and represented 16% of total Product Sales, down from 21% in 2017



Oncology. See page 50.



Cardiovascular, Renal and Metabolism. See page 56.



Respiratory. See page 62.

Global commercial presence, with strength in Emerging Markets (Product Sales)

Return to Growth from page 29.

Emerging Markets

$6,891m
33% of total
2017: $6,149m
2016: $5,794m

Product Sales increased by 12% (13% at CER). New Medicines represented 15% of Emerging Market sales in the year, up from 10% in 2017

US

$6,876m
33% of total
2017: $6,169m
2016: $7,365m

Product Sales increased by 11%. New Medicines represented 48% of Product Sales, up from 26% in 2017

Europe

$4,459m
21% of total
2017: $4,753m
2016: $5,064m

Product Sales declined by 6% (10% at CER), reflecting the entry of generic *Crestor* medicines in various markets in 2017 and continued competitive and price pressures

Established Rest of World

$2,823m
13% of total
2017: $3,081m
2016: $3,096m

Product Sales declined by 8% (9% at CER). New Medicines represented 24% of sales in the year, up from 13% in 2017. Performance reflected, in particular, the success of *Tagrisso* and *Forxiga*

Our talented employees

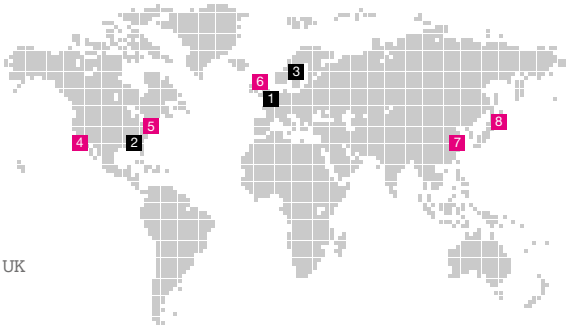
Committed to attracting, retaining and developing a talented and diverse workforce united in the pursuit of our Purpose and living our Values

Be a Great Place to Work from page 38.

64,600
employees
2017: 61,100
2016: 59,700

44.6%
of our senior roles are filled by women

102
manuscripts published by our scientists in high-impact peer-reviewed journals



Strategic R&D centres
1. Cambridge, UK (HQ)
2. Gaithersburg, MD, US
3. Gothenburg, Sweden

Other R&D centres
4. California, US
5. Boston, MA, US
6. Alderley Park and Macclesfield, UK
7. Shanghai, China
8. Osaka, Japan

A sustainable business

Committed to operating in a way that recognises the interconnection between business growth, the needs of society and the limitations of our planet

Sustainability from page 42.

Priority
1
Broadening access to healthcare

Priority
2
Furthering ethics and transparency

Priority
3
Protecting the environment

100%
of employees trained in Code of Ethics

CDP DRIVING SUSTAINABLE ECONOMIES

MEMBER OF Dow Jones Sustainability Indices In Collaboration with RobecoSAM

access to medicine index

Our capital allocation priorities

Striking a balance between the interests of the business, our financial creditors and shareholders, and supporting our progressive dividend policy

Financial Review from page 74.

Distributions to shareholders	Dividends	Proceeds from issue of shares	Total
	$3,484m 2017: $3,519m 2016: $3,561m	$(34)m 2017: $(43)m 2016: $(47)m	$3,450m 2017: $3,476m 2016: $3,514m

Dividend per Ordinary Share for 2018	1st interim dividend	2nd interim dividend	Total
	$0.90 Pence: 68.4 SEK: 7.92 Payment date: 10 September 2018	$1.90 Pence: 146.8 SEK: 17.46 Payment date: 27 March 2019	$2.80 Pence: 215.2 SEK: 25.38 2017: $2.80 2016: $2.80

Chairman's Statement

In 2013, your Board chose a very clear strategic route to follow. It was a strategy rooted in our heritage as a company focused on innovative science to deliver great medicines.

"We succeeded because we have been true to our Value of following the science. We also succeeded because we put patients first."

In 2018, under the leadership of Pascal Soriot, and together with the entire talented AstraZeneca team, we delivered on our promise and returned a reinvigorated AstraZeneca to Product Sales growth.

Delivering for patients

We succeeded because we have been true to our Value of following the science. We also succeeded because we put patients first. This will become increasingly important as more people take an active role in managing their health and new technologies empower them to make their own health choices. In visits around the world, I have seen how digital technology is transforming the way we work and has the potential to help us develop better medicines, faster and with clearer benefits for patients and value for society.

A changing world

We also need to show leadership in responding to other ways in which our world is changing: the increasing burden of non-communicable diseases, especially in poorer parts of the world; growing and ageing populations; and, notably, society's growing expectations of business. At the same time, we face more immediate challenges: the uncertainties surrounding the UK's impending departure from the EU, the trade dispute between the US and China, and other countries where we see a rise in disruptive politics.

Sustainable health

I believe that being a sustainable business is fundamental to overcoming these challenges, as well as our ability to deliver innovative medicines to patients and ensure people have access to them. We are committed to our role in delivering sustainable health and maximising the benefit of what we do for patients, broader society and the planet. I'm pleased that, once again, our efforts have been recognised by, for example, the Dow Jones Sustainability and World Indices and Access to Medicine Index.

Returns to shareholders and outlook

While we returned to Product Sales growth in 2018, that has yet to be reflected in our profitability, with Reported earnings per share (EPS) of $1.70 representing a decline of 28% (29% at CER) compared with 2017. This reflected a decline in Total Revenue and the Reported Gross Margin. Core EPS declined by 19% to $3.46, also driven by the investments we made in launching our new medicines. Core EPS for the final quarter rose, however, by 22% compared with the prior year quarter, reflecting Product Sales growth, higher ongoing Externalisation Revenue and a favourable adjustment to deferred taxes arising from recently announced reductions in Dutch and Swedish corporate income tax rates. Our guidance for 2019 is for an increase in Core EPS at CER to $3.50-3.70 as we anticipate a high single-digit percentage increase in Product Sales to underpin improved profitability.

In light of this, the Board reaffirmed its commitment to the progressive dividend policy, with a second interim dividend for 2018 of $1.90 per share, taking the unchanged full-year dividend per share to $2.80.

Appreciation

I would like to thank Pascal and everyone at AstraZeneca for all they have done to bring us to this point in our strategic journey. I am looking forward to the coming years when, by continuing to push the boundaries of science, we can bring more medicines to more patients and make a difference to more lives.

Leif Johansson
Chairman

Chief Executive Officer's Review

As we enter the next phase in our journey, the fundamentals of our strategy and plans remain unchanged, with Product Sales growth driving improved profitability and the generation of increasing levels of cash.

"…in 2018, after the previous six years in which revenues had fallen by more than one third, we turned the corner and returned to Product Sales growth."

New medicines launched since 2013

Oncology
- *Imfinzi* for lung and bladder cancer
- *Lynparza* for ovarian and breast cancer
- *Tagrisso* for lung cancer
- *Calquence* for mantle cell lymphoma
- *Lumoxiti* for hairy cell leukaemia

CVRM
- *Lokelma* for hyperkalaemia
- *Qtern* for diabetes

Respiratory
- *Fasenra* for severe asthma
- *Bevespi Aerosphere* for chronic obstructive pulmonary disease

In March 2013, shortly after I joined AstraZeneca, we set out our strategy to Achieve Scientific Leadership, Return to Growth and ensure we are a Great Place to Work. Five years on, thanks to the great work of every single one of my colleagues, we have made remarkable progress: our science-led strategy and our open and entrepreneurial culture are underpinning a resurgence in innovation that is fuelling sustainable Product Sales growth and delivering medicines that patients and society value and can access.

Product Sales growth

The first phase in our journey provided focus and galvanised the organisation behind rebuilding our pipeline. Having regained our scientific edge, the second stage was crucial as we drove our Growth Platforms forward, launched new medicines and made them available to patients. I am pleased to report that, in 2018, after the previous six years in which revenues had fallen by more than one third, we turned the corner and returned to Product Sales growth, driven by a new generation of medicines from our therapy areas.

As we look ahead through 2019 and beyond, continued investment in our product launches and pipeline should keep us on track to deliver sustainable and profitable growth in line with our targets. Consistent with this, we are reshaping the way we undertake research and development to bring new focus and impetus, accelerate the launches of new medicines and consolidate what is already one of the most exciting and productive pipelines in the industry. We are also reorganising our commercial operations to reflect our therapy area focus, maximise collaboration with our R&D organisation, and strengthen strategic planning and field force integration to support delivery of our medicines to patients.

Achieve Scientific Leadership

Our first priority for achieving scientific leadership was to focus on innovative science in three main therapy areas: Oncology; Cardiovascular, Renal and Metabolism (CVRM); and Respiratory. This has been our driving force all along, a focus reinforced by our recent organisational changes. In other disease areas, we have sought to maximise the value of our portfolio through licensing, collaboration and externalisation activity.

We also said we would rebuild our pipeline and, by 2015, had 15 new molecular entities (NMEs) in Phase III/Pivotal Phase II or under regulatory review compared with a target, set in 2013, of 10 by the end of 2016. In 2018, we had eight NMEs in Phase III/Pivotal Phase II or under regulatory review. The same year, we also made 28 regulatory submissions in major markets and received 23 approvals for our medicines. Both are record numbers for AstraZeneca. Of course, we know that in pushing the boundaries of science we will sometimes experience setbacks. In 2018, for example, there were disappointing Phase III trial results for six projects, including the MYSTIC trial of *Imfinzi* and tremelimumab in stage 4 non-small cell lung cancer (NSCLC). However, we remain confident in *Imfinzi* as the cornerstone of our immuno-oncology (IO) programme and continue to evaluate its potential in ongoing NSCLC trials, including *Imfinzi* and *Imfinzi* plus tremelimumab in combination with chemotherapy. Overall, we are on target for sustainably delivering two NMEs annually by 2020.

Chief Executive Officer's Review *continued*

23

23 NME and major LCM regional approvals – a record

84%

Five Growth Platforms represent 84% of Total Revenue

84%

84% of employees understand how they can contribute to our sustainability priorities

"...we are well on our way to exceeding our target of launching 10 major new medicines by 2020."

Finally, we are well on our way to exceeding our target of launching 10 major new medicines by 2020. The panel on the previous page shows how, since 2013, nine medicines have been launched from our three main therapy areas which are making a real difference to the lives of patients around the world. In 2018 alone, we delivered three new medicines – *Lumoxiti*, *Lokelma* and roxadustat. Roxadustat, for the treatment of chronic kidney disease (CKD) anaemia, is particularly noteworthy as it is the first time that a first-in-class medicine has been approved first in China. We expect it to be launched later in 2019.

Above all, we believe in what science can do. And it is a testament to the strength of our science that, in 2018, AstraZeneca scientists published 102 manuscripts (another record number) in 'high-impact' peer-reviewed journals – a 14-fold increase since 2012.

Return to Growth

In support of our Return to Growth priority, we said we would focus on five Growth Platforms: Oncology, New CVRM, Respiratory, Japan and Emerging Markets. In 2013, they represented less than half of sales and this had grown to 84% of Total Revenue by 2018. Overall, as shown in the table opposite, Product Sales in 2018 increased by 4% to $21,049 million (4% at CER), driven by strong growth in the last two quarters of the year – 8% and 5% respectively (9% and 8% at CER). This reflected the performance of our New Medicines[1], up by 81% (at CER) and adding $2.8 billion in incremental sales, as well as the sustained strength of Emerging Markets, up by 12% (13% at CER). Product Sales in China increased by 28% (25% at CER) in the year. Externalisation Revenue declined by 55% in the year to $1,041 million, partly driven by the impact of $1,247 million of income received during 2017 as part of our collaboration with MSD for *Lynparza*. Total Revenue declined by 2% (2% at CER) to $22,090 million.

We also said that we would leverage our global commercial presence and our strength in Emerging Markets. After four years of decline, the US returned to sales growth in 2018 while Product Sales in Emerging Markets, which represented 21% of sales in 2013, amounted to 33% of Product Sales. Emerging Markets now represent our largest Region by Product Sales.

[1] *Tagrisso*, *Imfinzi*, *Lynparza*, *Calquence*, *Lumoxiti*, *Brilinta*, *Farxiga*, *Lokelma*, *Bevespi* and *Fasenra*. These New Medicines are pillars in the three main therapy areas and important platforms for future growth.

Additionally, we wanted to shift to a balance of specialty and primary care medicines. Specialty care medicines now comprise all our Oncology medicines and *Fasenra*. They represented 30% of Product Sales in 2018 and sales increased by 57% in the year (56% at CER) to $6,325 million.

Be a Great Place to Work

Underpinning everything is our dedication to being a great place to work, with a talented and diverse team committed to living our Values and supported by an inclusive, learning culture. It is that team of people who drive our progress, and our employee (Pulse) surveys show that 94% of employees understand our strategy, 89% believe in it and 83% would recommend AstraZeneca as a great place to work – all statistics that place us among the leading companies in the world.

While there is always more we can do, 2018 also saw continued employee development and an increase in the representation of women in senior roles. More generally, we have implemented numerous initiatives, such as unconscious bias training, across the globe as part of our commitment to inclusion and diversity. We are therefore particularly proud to have been recognised as the only pharmaceutical company selected for the 2019 Bloomberg Gender-Equality Index which distinguishes companies committed to transparency in gender reporting and advancing women's equality.

More widely, 84% of employees understand how they can contribute to our sustainability priorities where our achievements include reaching 12 million people through our access to healthcare programmes and winning Ethical Corporation's Community Investment Program of the year award for Young Health – our global disease prevention programme. We know we can't achieve our goals alone. As a sustainable organisation we have an unwavering commitment to being a trusted partner for stakeholders, an excellent investment for shareholders, and an indispensable ally in the quest to meet the global healthcare challenge.

Global Product Sales by therapy area

	2018			2017			2016		
	Sales $m	**Actual growth %**	**CER growth %**	Sales $m	Actual growth %	CER growth %	Sales $m	Actual growth %	CER growth %
Oncology	**6,028**	**50**	**49**	4,024	19	19	3,383	20	20
Cardiovascular, Renal & Metabolism	**6,710**	**(8)**	**(8)**	7,266	(10)	(10)	8,116	(14)	(13)
Respiratory	**4,911**	**4**	**3**	4,706	(1)	(1)	4,753	(5)	(3)
Other Disease Areas	**3,400**	**(18)**	**(19)**	4,156	(18)	(17)	5,067	(20)	(19)
Total	**21,049**	**4**	**4**	20,152	(5)	(5)	21,319	(10)	(8)

Seizing the opportunities ahead

As we enter the next phase in our journey, the fundamentals of our strategy and plans remain unchanged, with Product Sales growth driving improved profitability and the generation of increasing levels of cash. Our focus will continue to be on innovative science and leadership in our three main therapy areas. And we will carry on leveraging our global presence and strength in emerging markets, while pursuing the development of strong, balanced portfolios of both specialty and primary care medicines.

As the Chairman indicated, the world around us is changing, so we too are shifting the way in which we deliver our strategy. Our emphasis is on growth through innovation – being more patient-centric, doing more with digital technology and data, and advancing more innovative science.

The new organisational structure we announced in January 2019 supports the next phase in our journey and is intended to enhance scientific innovation and commercial success. The changes further increase focus on our main therapy areas, integrate R&D functions for agile decision making and more flexible resource allocation, as well as increasing collaboration between our R&D and commercial units.

My colleagues

At the same time as making these changes, we announced the appointment of Dr José Baselga to lead our R&D unit for Oncology. José is an outstanding oncology leader with vast experience in the development of innovative cancer therapies. His research and clinical achievements have led to the development of several innovative medicines, and he is an international thought leader in cancer care and clinical research. José's expertise adds further scientific and leadership excellence to our already strong team and will help us to continue building a world-class R&D unit for Oncology.

Before this, we said goodbye to Bahija Jallal, EVP MedImmune, and Mark Mallon, EVP Global Product and Portfolio Strategy, Global Medical Affairs and Global Corporate Affairs, whose moves to become CEOs at two exciting biotech companies illustrated the talent that we have in AstraZeneca and how highly other companies regard our people. Sean Bohen, EVP for Global Medicines Development and Chief Medical Officer will also be leaving following the leadership structure changes. I would like to thank Bahija, Mark and Sean for the important roles they played in AstraZeneca's return to growth.

Finally, my thanks go to all my colleagues in AstraZeneca. We have been on an incredible journey. None of this would have been possible without the talented people we have in the organisation. I thank them all for everything they have done as, together, we embark on the next phase in this great Company's journey.

Pascal Soriot
Chief Executive Officer

Business model and life-cycle of a medicine

AstraZeneca at a glance summarises our business. In this section, we review our business model – how we create financial value and the resources we need in order to bring benefits to patients.

Why AstraZeneca

We are a global pharmaceutical business which has:

> A science-led innovation strategy
> An R&D platform across small molecules and biologics
> Three main therapy areas: Oncology; Cardiovascular, Renal and Metabolism; and Respiratory
> A portfolio of specialty care and primary care medicines
> A global footprint

Who we are

Our Purpose

We push the boundaries of science to deliver life-changing medicines.

Our Purpose underpins everything we do. It gives us a reason to come to work every day. It reminds us why we exist as a Company. It helps us deliver benefits to patients and create value for shareholders.

Our Values

We follow the science.
We put patients first.
We play to win.
We do the right thing.
We are entrepreneurial.

Our Values determine how we work together and the behaviours that drive our success. Our Values guide our decision making, define our beliefs and foster a strong AstraZeneca culture.

Our Sustainability

We are committed to operating in a way that recognises the interconnection between business growth, the needs of society and the limitations of our planet.

Our sustainability priorities in health, ethics and the environment support the delivery of our business strategy.

Business Review from page 24.

What we do

Our business activities span the entire life-cycle of a medicine.

How we create financial value

Investment

We invest in the discovery, development, manufacturing and commercialisation of our pipeline of innovative small molecule and biologic prescription medicines, including targeted business development through collaboration, in-licensing and acquisitions.

Revenue generation

We generate revenue from Product Sales of our existing medicines and Growth Platform launches, as well as from our externalisation activities. Our focus is on creating products that facilitate profitable future revenue generation, while bringing benefits to patients.

Reinvestment

We reinvest in developing the next generation of innovative medicines and in our Growth Platforms that provide the platform for future sources of revenue in the face of recent losses of key patents.

Life-cycle of a medicine

Research and development phases 5–15 years

1. Find potential medicine
> Identify unmet medical need aligned with our three therapy areas and undertake scientific research to identify potential new medicines.
> Initiate process of seeking patent protection.

2. Pre-clinical studies
> Conduct laboratory and animal studies to understand if the potential medicine is safe to introduce into humans and in what quantities.
> Determine likely efficacy, side effect profile and maximum dose estimates.

3. Phase I studies
> Begin clinical studies with small groups of healthy human volunteers (small molecules) or patients (biologics) to understand how the potential medicine is absorbed into the body, distributed around it and excreted.
> Determine approximate dosage and identify side effects.

4. Phase II studies
> Conduct studies on small- to medium-sized groups of patients to test effectiveness and tolerability of the medicine and determine optimal dose.
> Design Phase III studies to generate data needed for regulatory approvals and pricing/reimbursement globally.

5. Phase III studies
> Engage in studies in a larger group of patients to gather information about effectiveness and safety of the medicine and evaluate the overall benefit/risk profile.
> Initiate branding for the new medicine in preparation for its launch.

6. Regulatory submission and pricing
> Seek regulatory approvals for manufacturing, marketing and selling the medicine.
> Submit clinical data to regulatory authorities (and, if requested, generate further data increasingly in real-world settings) to demonstrate the safety and efficacy of the medicine to enable them to decide on whether to grant regulatory approvals.

Launch phase 5–15 years

7. Launch new medicine
> Raise awareness of patient benefit and appropriate use, market and sell medicine.
> Clinicians begin to prescribe medicines and patients begin to benefit.
> Continuously monitor, record and analyse reported side effects. Review need to update the side effect warnings to ensure that patients' wellbeing is maintained.
> Assess real-world effectiveness, and opportunities to support patients and prescribers, to achieve maximum benefit from the medicine.

8. Post-launch research and development
> Conduct studies to further understand the benefit/risk profile of the medicine in larger and/or additional patient populations.
> Life-cycle management activities to broaden understanding of a medicine's full potential.
> Consider additional diseases or aspects of disease to be treated by or better ways of administering the medicine.
> Submit data packages with requests for life-cycle management to regulatory authorities for review and approval.

Post-exclusivity 20+ years

9. Post-exclusivity
> Patent expiry and generic entry.
> Reinvestment of returns.

Note: This is a high-level overview of a medicine's life-cycle and is illustrative only. It is neither intended to, nor does it, represent the life-cycle of any particular medicine or of every medicine discovered and/or developed by AstraZeneca, or the probability of success or approval of any AstraZeneca medicine.

Business model and life-cycle of a medicine *continued*

What does our business model require to be successful?

A talented and diverse workforce
We need to acquire, retain and develop a talented and diverse workforce united in pursuit of our Purpose and Values and fostering a strong AstraZeneca culture.

See Employees from page 38.

64,600
employees

A leadership position in science
We need to achieve scientific leadership if we are to deliver life-changing medicines. To that end, we need to focus on innovative science, prioritise and accelerate our pipeline and transform our innovation and culture model.

See Achieve Scientific Leadership from page 25.

$5.9bn
invested in our science

Effective partnerships
We need business development, specifically partnering, which is an important element of our business model. It supplements and strengthens our pipeline and our efforts to achieve scientific leadership.

See Partnering on page 35.

>630
collaborations worldwide

Commercialisation skills
We need a strong global commercial presence and skilled people to ensure that we can successfully launch our medicines, that they are available when needed and that patients have access to them.

See Return to Growth from page 29.

>100
countries in which we are active

Intellectual property (IP)
We need to create and protect our IP rights. Developing a new medicine requires significant investment over many years, with no guarantee of success. For our investments to be viable, we seek to protect new medicines from being copied for a reasonable period of time through patent protection.

See Intellectual Property from page 35.

>100
countries where we obtain patent protection

A robust supply chain
We need a supply of high-quality medicines, whether from one of the 29 Operations sites in 17 countries in which we manufacture or the $13 billion we spend on the purchase of goods, services and active pharmaceutical ingredients (APIs).

See Operations and Supply chain management from page 33.

$13bn
spent with suppliers

Financial strength
We need to be financially strong, including having access to equity and debt finance, to bear the financial risk of investing in the entire life-cycle of a medicine.

See Financial Review from page 74.

$2.6bn
net cash flow from operating activities

How we add value

Improved health
Continuous scientific innovation is vital to achieving sustainable healthcare which creates value by:

> improving health outcomes and transforming patients' lives
> enabling healthcare systems to reduce costs and increase efficiency
> improving access to healthcare and healthcare infrastructure
> helping develop the communities in which we operate through local employment and partnering.

Financial value
Revenue from our Product Sales and externalisation activities generates cash flow, which helps us:

> fund our investment in science and Growth Platforms to drive long-term value
> follow our progressive dividend policy
> meet our debt service obligations.

This involves balancing the interests of our business, financial creditors and shareholders.

See Financial Review from page 74.

Marketplace

Economic growth, an expanding global population and technological change are expected to contribute to growth in the pharmaceutical industry. However, social, economic and political challenges remain in meeting unmet medical need.

A changing world

> NCDs kill 41 million people each year, disproportionately affecting low- and middle-income countries
> Growing and ageing populations, with increasing urbanisation
> Breakthroughs in digital and other technologies transforming the pharmaceutical industry

Increasing demand for healthcare

> The US is the largest pharmaceutical market, with 47% of global sales
> Pharmaceutical sales growth of 4.4% in 2018, led by emerging markets
> Expected growth to 2022 will be led by the US and developing markets but with slower growth in China

Pharmaceutical sector opportunities and challenges

> Pricing, regulation and patent exclusivity present opportunities as well as challenges
> The sector is reshaping itself at the same time as it seeks to develop trust with key stakeholders

A changing world

Society is changing

Increasing burden of chronic disease
An ageing population and changes in society are contributing to steady increases in non-communicable diseases (NCDs) with developing countries particularly affected as their populations grow. As the burden of NCDs grows, so do public expectations while governments' ability to meet them is constrained as finances are under stress. Low- and middle-income countries are also disproportionately affected by issues such as air pollution and climate change, thereby exacerbating social, economic and demographic inequalities.

Growing societal expectation of businesses
Society's views of business are changing with organisations no longer valued solely on the quality of products and services and financial performance, but also their engagement with employees, customers, communities and society as a whole. Workforce dynamics are also changing for many as working for a single employer is replaced by working independently in a number of different roles.

$47tn
The WHO estimates that NCDs kill 41 million people each year and could cost the global economy $47 trillion by 2030.

75%
NCDs disproportionately affect people in low- and middle-income countries where more than three quarters of global NCD deaths – 32 million – occur.

57%
Between 2001 and 2020, the WHO estimates that chronic diseases will have increased by 57%.

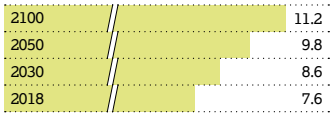
A changing world *continued*

Global growth is shifting

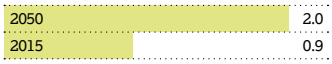
Growing and ageing populations, increasing urbanisation
As shown on the right, patient populations are expanding. For example, the world's population is rising and more people are living in cities, with an estimated three million people a week moving to cities in 2015. Urbanisation presents opportunities, such as greater wealth and access to better healthcare, but also new hazards and healthcare challenges, such as an increase in the prevalence of NCDs. These diseases include cancer and cardiovascular, metabolic and respiratory diseases which are often associated with urban lifestyle choices, including smoking, diet and lack of exercise. NCDs are also associated with ageing and, with the majority of the world's workforce rapidly ageing, healthcare costs are rising as people are living longer. In many markets, ageing populations mean the size of the labour force will stagnate or decline, resulting in a potential shortage of labour compared with the abundance of labour that has fuelled growth since the 1970s. On the other hand, and as outlined below, technology is transforming the workplace.

Strong global economic growth, driven by Eastern economies
With the rapid urbanisation of developing markets, such as China and India, economic growth is shifting east and away from advanced economies such as North America, Western Europe and Japan. By some estimates, Africa could represent the fourth largest economy in the world by 2040 and, by 2050, India could overtake the US as the second largest economy. So far as shorter-term economic trends are concerned, the October 2018 World Economic Outlook of the International Monetary Fund (IMF) continued to forecast strong economic growth. However, it cautioned that "the balance of risks… has shifted to the downside in a context of elevated policy uncertainty".

Estimated world population (UN, bn)



Estimated population over the age of 60 (WHO, bn)



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3m
Three million people per week estimated to have moved to cities in 2015.

80%
By 2050, 80% of all older people will live in low- and middle-income countries.

Digital and technical breakthroughs

Advances in digitisation, analytics, artificial intelligence (AI) and automation are redefining how business and industries work. They will transform the workplace and business processes as people interact with increasingly smarter machines.

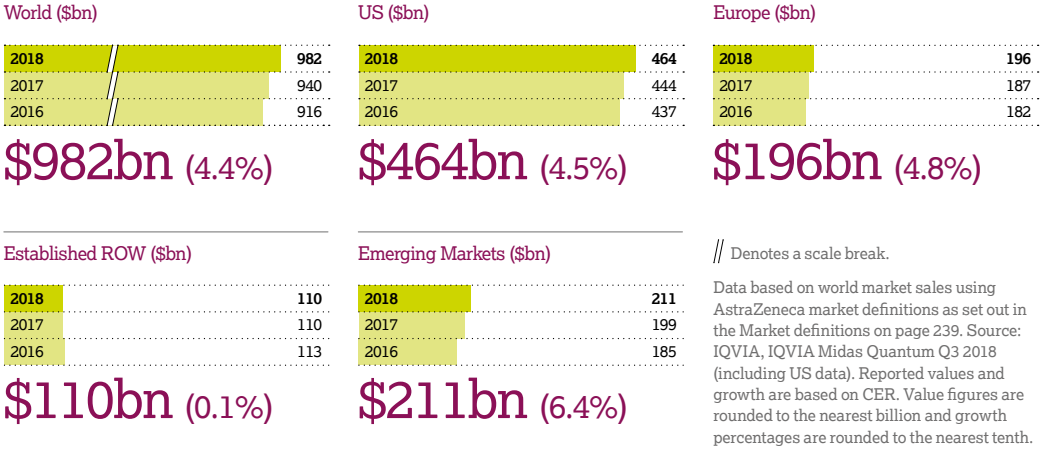
New entrants from the technology sector are bringing different competencies to healthcare, applying their knowledge to accelerate scientific discovery, improve health through technology and better understanding the consumer. At the same time, and enabled by technology, patients are becoming more engaged and willing to take greater control of their health and treatment choices.

> "New entrants from the technology sector are bringing different competencies to healthcare… and enabled by technology, patients are becoming more engaged and willing to take greater control of their health and treatment choices."

Increasing demand for healthcare

Global pharmaceutical sales

As shown in the chart on the right, global pharmaceutical sales grew by 4.4% in 2018. Established Markets saw an average revenue increase of 3.9% and Emerging Markets revenue grew at 6.4%. The US, China, Japan, Germany and France are the world's top five pharmaceutical markets by 2018 sales. In 2018, the US had 47.2% of global sales (2017: 47.2%; 2016: 47.7%).



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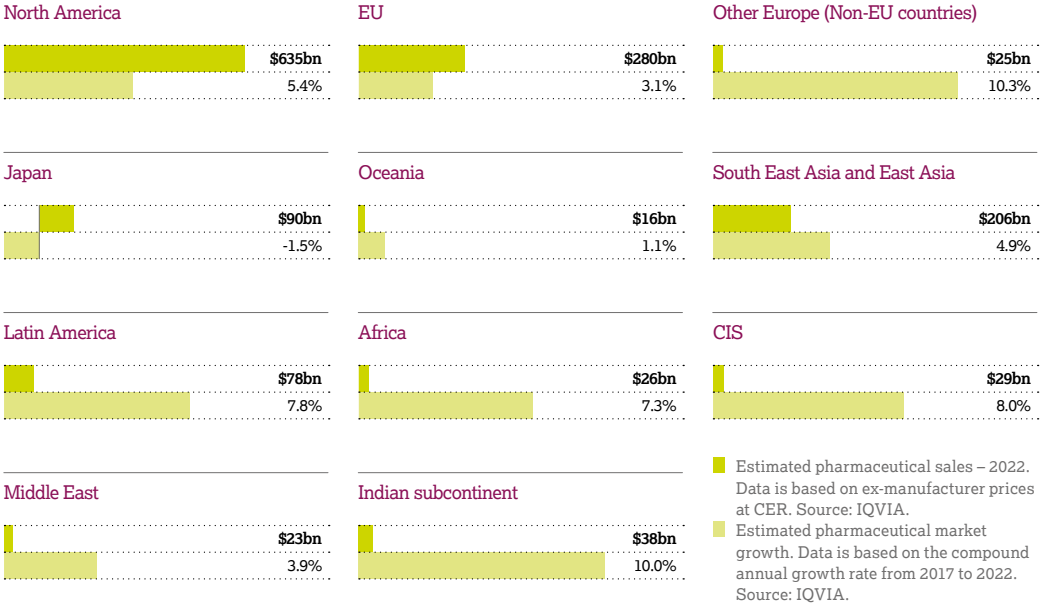
Data based on world market sales using AstraZeneca market definitions as set out in the Market definitions on page 239. Source: IQVIA, IQVIA Midas Quantum Q3 2018 (including US data). Reported values and growth are based on CER. Value figures are rounded to the nearest billion and growth percentages are rounded to the nearest tenth.

Estimated pharmaceutical sales and market growth – 2022

The table on estimated pharmaceutical sales and market growth to 2022 on the right also illustrates that we expect the established markets in North America and developing markets, including Africa, CIS, Indian subcontinent and Latin America, to fuel pharmaceutical growth. Market growth in China is expected to remain below historical levels at a compound annual growth rate of 4.6%. This is due to the continued slowdown of the major hospital sector.



- Estimated pharmaceutical sales – 2022. Data is based on ex-manufacturer prices at CER. Source: IQVIA.
- Estimated pharmaceutical market growth. Data is based on the compound annual growth rate from 2017 to 2022. Source: IQVIA.

Pharmaceutical sector opportunities and challenges

In addition to the global trends set out on the previous pages, we also face a number of opportunities and challenges within the pharmaceutical sector, as set out below. Our strategy reflects our response to this environment and, where applicable, the relevant strategic response to each trend is highlighted below.

For more information, see Strategy from page 18, Key Performance Indicators from page 20, Achieve Scientific Leadership from page 25, Return to Growth from page 29 and Be a Great Place to Work from page 38.

Advances in science and medicine

Scientific innovation is critical to addressing unmet medical need. The delivery of new medicines will rely on a more advanced understanding of the underlying biology of the disease, and the use of new technology and approaches. These include genomics and digital healthcare. Scientific and technological breakthroughs in small molecules and in biologics are also helping accelerate innovation. Innovation will be accelerated through the use of large volumes of biological data from disease biology and genomics which is driving precision medicine, while advances in data management and data integration are improving the speed and quality of clinical trial processes. Such advances have resulted in increased numbers of FDA Priority Reviews and Breakthrough designations.

The cost of developing new medicines continues to rise with annual global R&D investment estimated to be $150-160 billion. Regulators and payers are demanding greater evidence of the comparative effectiveness of medicines. On the other hand, a greater emphasis on Proof of Concept is helping to improve productivity and reduce costs by showing the potential efficacy of drugs earlier in the development process. Against this background, the FDA approved 59 novel drugs in 2018 compared with 46 in 2017 and 22 in 2016. Nevertheless, the risk of any products failing at the development or launch stages, or not securing regulatory approvals, continues.

$150-160bn
Annual global R&D investment estimated to be $150-160 billion.

59
The FDA approved 59 novel drugs in 2018 compared with 46 in 2017 and 22 in 2016.

Link to strategy
Achieve Scientific Leadership

For more information, see Risk from page 220.

Regulatory environment

The public's expectation of safe, effective and high-quality medicines is reflected in a highly regulated biopharmaceutical industry. At the same time, we are seeing instances of government policy and regulation being introduced to stimulate innovation in drug development, and of regulatory health authorities implementing programmes intended to speed up patient access to transformative medicines. Examples include the 21st Century Cures Act of 2016 and the FDA Reauthorization Act of 2017 in the US, a new conditional early approval system in Japan and proposed changes to regulations in China.

In addition, international harmonisation of regulatory requirements is being advanced in many areas through organisations such as the International Council for Harmonization (ICH), the Pharmaceutical Inspection Cooperation Scheme (PIC/S), the Pan American Network for Drug Regulatory Harmonization (PANDRH), and the International Conference of Drug Regulatory Authorities (ICDRA).

There are also uncertainties. In Europe, they include how the UK will work with the EU regulatory system following its planned exit from the EU, the approach the UK will take to establishing its own regulatory system outside the EU, and the relocation of the EMA from London to Amsterdam, Netherlands (and the likely disruption this will cause to regulatory processes).

The implementation of the EU Clinical Trials Regulation has also been delayed. Nevertheless, paediatrics and use of digital tools in clinical development, as well as patients' access to innovative medicines and stakeholders' interactions to improve drug development, are high on the EU agenda.

In biosimilar development, regulatory requirements for the registration of biosimilar products are becoming better defined. However, significant areas of regulatory policy are still evolving. Among these are transparency of data regarding the level of evidence to support approval of claims for biosimilarity in labelling, standards for interchangeability and pharmaceutical substitution, and traceability of pharmacovigilance reports through naming conventions that permit differentiation of products.

Increased transparency of data used for regulatory decision making continues to be an area of interest to regulatory authorities in the EU and the US. It has recently attracted interest elsewhere, such as in Canada. We believe that transparency enhances the scientific understanding of how our medicines work and is in the medical interest of our patients.

"We believe that transparency enhances the scientific understanding of how our medicines work and is in the medical interest of our patients."

Link to strategy
Achieve Scientific Leadership

For more information, see Risk from page 220. For more information about biosimilars, see Loss of exclusivity and genericisation opposite.

Pricing of medicines

Pricing and reimbursement remain challenging in many markets. We continue to see examples where healthcare services (including pharmaceuticals) are highly regulated by governments, insurers and other private payers through various controls on pricing and reimbursement. Implementation of cost-containment reforms and shifting market dynamics are further constraining healthcare providers, while difficult economic conditions burden patients who have out-of-pocket expenses relating to their medicines. Pharmaceutical companies are now expending significant resources to demonstrate the economic as well as the therapeutic value of their medicines.

The need and desire for payers to manage drug expenditure has been heightened by the shift over the last decade from a primary care to a specialty care focus. Specialty drugs are used for the treatment of complex, chronic or rare conditions such as cancers, and pricing for these products reflects the higher value they bring to patients and payers, as well as the smaller patient numbers as a result of targeted treatment options.

Pricing controls and transparency measures remain a priority in key markets such as China, where the National Reimbursement Drug List (NRDL) was updated in 2017. In Europe, governments continue to implement and expand price control measures for medicines, and the EU has committed to introducing a harmonised HTA review. In other markets, there has been a trend towards rigorous and consistent application of pricing regulations, including reference pricing and group/alliance purchasing.

There is also pressure on pricing in the US. For example, federal and state policymakers are considering legislative and regulatory efforts to lower drug prices and to implement transparency measures. While legislative efforts to repeal and replace the Affordable Care Act (ACA) have not been successful, the current administration and members of Congress remain focused on healthcare policy priorities, including efforts to increase competition and generic drug use in government programmes, which could create downward pressure on pricing. The healthcare industry may also be used as a means to offset government spending. US federal agencies continue to propose and implement policies and programmes with the goal of reducing costs, increasing transparency, transforming the delivery system, and improving quality and patient outcomes.

"We continue to see examples where healthcare services (including pharmaceuticals) are highly regulated by governments, insurers and other private payers through various controls on pricing and reimbursement."

Link to strategy

Return to Growth

For more information, see Risk from page 220.

Loss of exclusivity and genericisation

Patent protection for pharmaceutical products is finite and, after protection expires, payers, physicians and patients gain greater access to generic alternatives (both substitutable and analogue) in many important drug classes. These generic alternatives are primarily lower priced because generic manufacturers are largely spared the costs of R&D and market development. As a result, demand for generics is high. For prescriptions dispensed in the US in 2018, generics constituted 84.8% of the market by volume (2017: 84.9%).

Generic competition can also result from patent disputes or challenges before patent expiry. Increasingly, generics companies are launching products 'at risk', for example, before resolution of the relevant patent litigation. This trend, which is likely to continue, creates significant market presence for the generic version while the litigation remains unresolved. Given the unpredictable nature of patent litigation, some companies have settled such challenges on terms acceptable to the innovator and generic manufacturer. While competition authorities generally accept such agreements as a legitimate way to settle these disputes, they have questioned some settlements as being anti-competitive.

Biologics typically retain exclusivity for longer than traditional small molecule pharmaceuticals, with less generic competition. With limited experience to date, the substitution of biosimilars for the original branded product has not followed the same pattern as generic substitution in small molecule products and, as a result, erosion of the original biologic's branded market share has not been as rapid. This is due to biologics' complex manufacturing processes and the inherent difficulties in producing a biosimilar, which could require additional clinical trials. However, with regulatory authorities in Europe and the US continuing to implement abbreviated approval pathways for biosimilar versions, innovative biologics are likely to face increased competition. Like biologics, some small molecule pharmaceutical products are in complex formulations and/or require technically challenging manufacturing and thus may not follow the pattern of generic market erosion seen with traditional, tableted pharmaceuticals. For those products, the introduction of generic alternatives (both substitutable and analogue) can be slower.

84.8%

For prescriptions dispensed in the US in 2018, generics constituted 84.8% of the market by volume (2017: 84.9%).

Link to strategy

Return to Growth

For more information, see Intellectual Property from page 35.

Pharmaceutical sector opportunities and challenges *continued*

Trust

The pharmaceutical industry continues to face challenges in building and maintaining its reputation and the trust of its stakeholders. This reflects past sales and marketing practices, pricing practices by some, as well as legal disputes between pharmaceutical companies and government and regulatory authorities.

Companies, including those in the pharmaceutical industry, have been investigated by the China Public Security Bureau following allegations of bribery, and criminal and financial penalties have been imposed. In the US, investigations by the US Department of Justice (DOJ) and Securities and Exchange Commission (SEC) under the Foreign Corrupt Practices Act continue, as do investigations by the UK Serious Fraud Office under the UK Bribery Act.

To address these challenges, companies are seeking to:

> embed a culture of ethics and integrity
> adopt higher governance standards
> promote sustainability programmes, particularly focused on access to healthcare
> improve relationships with employees, shareholders and other stakeholders.

Companies are also adopting more 'patient-centric' approaches that go 'beyond the pill' to encompass all aspects of disease management – prevention, screening, diagnosis, treatment and rehabilitation.

More generally, to be trusted by stakeholders, companies need to operate in a way that meets their expectations.

"The pharmaceutical industry continues to face challenges in building and maintaining its reputation and the trust of its stakeholders."

Link to strategy

Be a Great Place to Work

For more information, see Ethics and transparency from page 43.

Reshaping of the sector

Our competitors include large, research-based pharmaceutical companies (like AstraZeneca) that discover, develop and sell innovative, patent-protected prescription medicines and vaccines, smaller biotechnology and vaccine businesses, and companies that produce generic medicines. The pharmaceutical market is highly competitive. For example, the global respiratory market is likely to see changes with new branded or generic products with new combinations and devices. In immuno-oncology, the large number of clinical trials being carried out highlight the competitive nature of this area.

While our peers face similar challenges and opportunities, they approach them in different ways. Some companies have pursued a strategy focused on branded prescription pharmaceuticals. Others have diversified by acquiring or building branded generics businesses or consumer portfolios, or have looked to geographic expansion, especially in Emerging Markets. Companies are also focused on improving R&D productivity and operational efficiency. Across the industry, consolidation, business development deals (including licensing and collaborations) and competition for business development opportunities have continued.

The speed of technological change may also transform current business models. Existing and new entrants to the sector, for example from the technology sector, are focusing on patient outcomes rather than just products and services, prediction and prevention rather than just diagnosis and treatment. This may also entail new ways of competing.

The sustainability and growth of a more 'patient-centric' pharmaceutical industry is predicated on organisations being able to take full advantage of these breakthroughs in digital and other technologies.

"Existing and new entrants to the sector are focusing on patient outcomes rather than just products and services, prediction and prevention rather than just diagnosis and treatment."

Link to strategy

Global, science-led pharmaceutical company

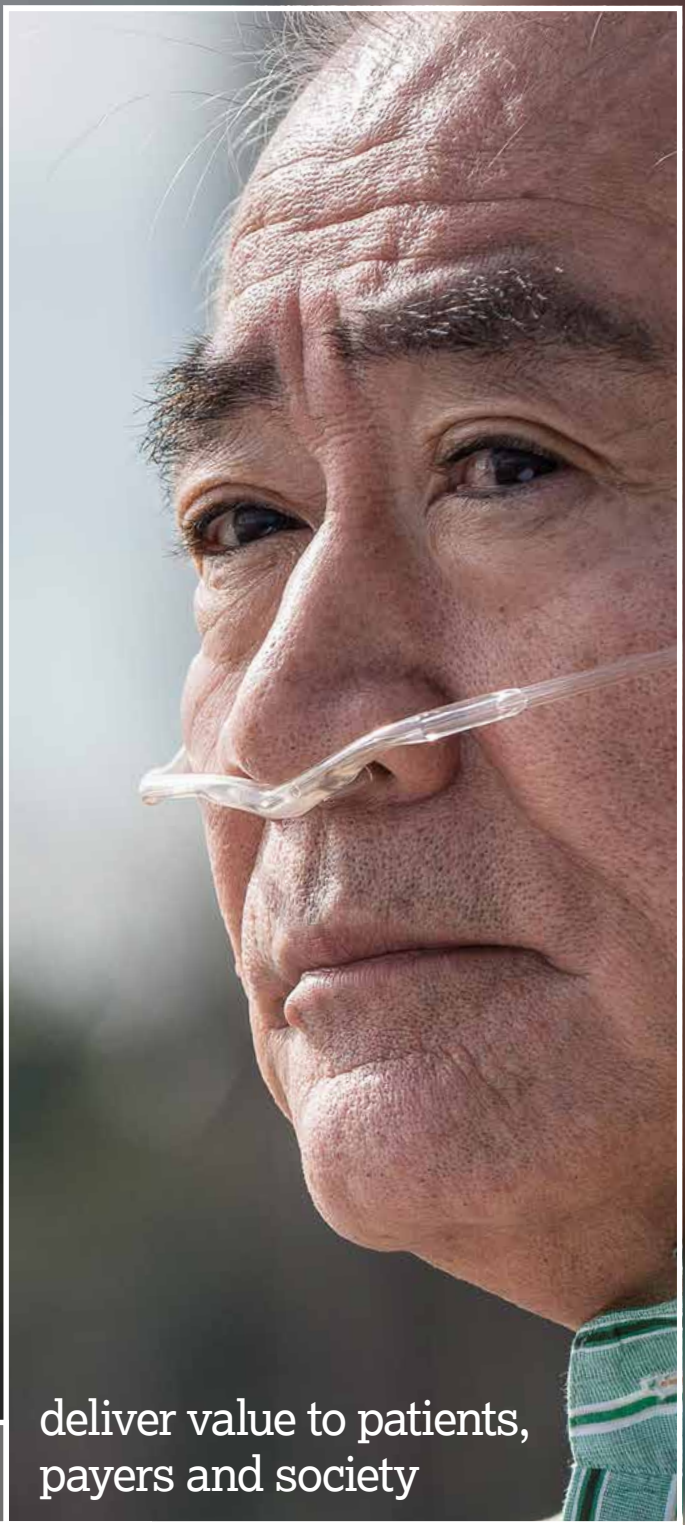
For more information, see Risk from page 220.

One of the approaches we are adopting to payment for our medicines is the implementation of Innovative Value Strategies, which link payment for a medicine to its effectiveness and the outcomes it achieves for patients, payers and society. For example, in the US we have entered into 37 agreements that span across each of our main therapy areas.

Scientific advances have led to a new era of medicines that have the potential to be used across different disease areas and patient populations. Value delivered by a medicine may differ across different indications and may not align to a single price. Additive pricing of combinations may also present an access challenge for health systems.

As part of our Innovative Value Strategies, we are working with payers and healthcare systems to introduce indication-based pricing (IBP) which aligns payment to value at the indication level. This development is part of our commitment to working with all stakeholders to improve patient health and adding value to the health system through innovative personalised medicines that are both accessible and affordable.

IBP requires three elements: a system of value assessment at the individual indication level; appropriate evidence that allows usage per indication to be linked to payment; and an ability to implement confidential commercial agreements that recognise the different value of individual indications. A number of countries have already implemented various IBP approaches, including the US, Australia, Italy and Switzerland.



Science *can* deliver value to patients, payers and society

~75%
of oncology medicines are expected to have multiple indications by 2020

50%
this is a 50% increase vs 2014

For more information on the principles on which we base the price of our medicines, see page 30.

We announced our strategy for returning to growth in 2013. The first phase in our journey was focused on rebuilding our pipeline. The second stage was crucial as we drove our Growth Platforms forward, continued to launch new medicines and made them available to patients. We returned to Product Sales growth in 2018 and, as we look ahead to 2020 and beyond, continued investment in our product launches and pipeline will keep us on track to deliver sustainable growth in line with our targets.

Our strategic priorities

We are a 'pure-play', global, science-led pharmaceutical company. We are focused on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of unmet medical need in three main therapy areas: Oncology; Cardiovascular, Renal and Metabolism; and Respiratory. In 2018, our strategic priorities were focused under the three pillars listed below.

1. Achieve Scientific Leadership

We are focusing our science on three therapy areas and accelerating our pipeline. We are also transforming our way of working.

2. Return to Growth

We are focusing on our Growth Platforms and transforming the business through specialty care, devices and biologic medicines. Targeted business development reinforces our efforts.

3. Be a Great Place to Work

We are evolving our culture and simplifying our business. We want to attract and retain the best talent.

We also want to do business sustainably.

Achieve Group Financial Targets

Effective delivery of our three strategic pillars will help us achieve our financial targets. We aim to deliver great medicines to patients while maintaining cost discipline and a flexible cost base. We wish to maintain a progressive dividend policy and a strong balance sheet.

How we report our progress

Key Performance Indicators (KPIs)

The following pages present our KPIs for 2018. Our KPIs are aligned to our three strategic priorities and are the indicators against which we measure our productivity and success. We also monitor financial targets, which indicate whether we have delivered our strategy in a way that allows us to continue to operate as a successful business.

Our remuneration arrangements are also aligned to our strategic priorities as set out in our Group scorecard and reflected in our KPIs. Achieve Scientific Leadership, Return to Growth and Achieve Group Financial Targets are included in the annual bonus targets.

For more information, see the Directors' Remuneration Report from page 120.

Strategic Report

Our operating model comprises key business functions that are aligned to delivery of our strategy. In addition, our therapy areas provide strategic direction for each of our disease areas all the way from early-stage development to commercialisation. Our Strategic Report therefore encompasses two types of review and our Principal Risks:

Business Review

Provides information on key activities and progress within each of the three strategic pillars. Within this section we report on our pipeline, the key business functions that are integral to delivering our strategy (R&D and Commercial), as well as those that we see as vital strategic enablers (Partnering and Operations) or which underpin our business model (Intellectual Property). We also report on our employees and how we do business sustainably.

Therapy Area Review

Looks at each of our therapy areas, their developments and focus for 2018, as well as what is in the pipeline.

Risks

We also review the risks that might challenge the delivery of our strategy.

For more information, see Business Review from page 24, Therapy Area Review from page 50 and Risk Overview from page 70.

How our current strategy responds to market trends

Our strategy reflects the way we have chosen to respond to the opportunities and challenges posed by the environment in which we operate, together with our competition, as outlined in Marketplace from page 11.

Strategic Priority	How are we responding to our environment?
1. Achieve Scientific Leadership	> Focus on innovative science in three therapy areas, a range of drug modalities, emerging drug platforms and new technologies. > Strengthen our ability to match targeted medicines to patients who need them most. > Drive R&D productivity by focusing on quality rather than quantity at all stages of drug discovery and development, and leveraging technology including the provision of enhanced data and clinical insights. > Partner with academia, governments, industry and scientific organisations to: – allow us to access the best and most advanced science and technology, and drive innovation – streamline regulatory processes, define and clarify approval requirements for innovative drug and biologic products. > Maintain effective working relationships with health authorities worldwide, including the FDA in the US, the EMA in the EU, the PMDA in Japan, ANVISA in Brazil and the NMPA in China. > Make information about our clinical research publicly available and work with regulators and other stakeholders to ensure the appropriate level of data transparency.
2. Return to Growth	> Engage with policymakers to support improvements in access, coverage, care delivery, quality of care and patient care outcomes. > Leveraging technology across prevention and awareness, diagnosis, treatment and wellness to deliver better patient outcomes more efficiently. > Enable our Emerging Markets to deliver better and broader patient access through innovative and targeted equitable pricing strategies and practices. > Partner with industry, governments and academia to find ways to bring new medicines to market more quickly and efficiently. > Evaluate the use of real-world evidence to further bolster the evidence base around therapeutic and economic value. > Base pricing policy on four principles: value, sustainability, access and flexibility. > Consider innovative outcomes contracts with payers as a mechanism to pay for value. > Pursue a strong patent strategy – from building robust patent estates that protect our pipeline and products to defending and enforcing our patent rights.
3. Be a Great Place to Work	> Our Code of Ethics is built on a refusal to tolerate bribery or any other form of corruption. > Further ethics and transparency, and broaden access to healthcare: two of our sustainability priorities. > As a values-led organisation, we are able to recruit the best talent which underpins our innovation and growth. > Engender a high-performing culture and lifelong learning. > Harness different perspectives, talents and ideas as well as ensuring that our employees reflect the diversity of the communities in which we operate.

Looking ahead – Beyond 2020

As we deliver the science-led transformation of our Company, developments are taking place that are changing the world in which our patients and employees live, and the environment and sector in which we operate. Looking to the future, we are considering the opportunities and challenges that these developments present and factoring them into our plans. For example, how do we:

> respond to an increased prevalence in NCDs, urbanisation and economic growth shifting east?
> maximise the opportunities arising from changing workforce dynamics and improve productivity with an ageing workforce?
> capitalise on digital and technological advances?
> connect better with patients who are taking a more active role in managing their own health?
> meet the challenges posed by the rise of social enterprise and sustainable development?

Questions such as these were among those discussed at our Board's formal annual strategy review day as they considered the fitness for purpose of our strategy beyond 2020. The preparation for this year's review included the crowdsourcing of ideas from employees as an input into those deliberations.

For more information on Board engagement with employees, see page 99.

Key Performance Indicators

Strategic priorities

Key Performance Indicators

Achieve Scientific Leadership

Focus on innovative science in three main therapy areas
Focus on Oncology; Cardiovascular, Renal and Metabolism; and Respiratory. We are also selectively active in autoimmunity, infection and neuroscience.

Work across small molecules, oligonucleotides and other emerging drug platforms, as well as biologic medicines, including immunotherapies, and innovative delivery devices that can offer choice to patients.

Prioritise and accelerate our pipeline
Accelerate and invest in key R&D programmes. At the end of 2018, eight NMEs were in Phase III/pivotal Phase II or under regulatory review, covering 15 indications.

Three NMEs were approved in 2018. Having met the targets for 2016 we had set ourselves in 2013, we are now on target to meet our longer-term goal of sustainably delivering two NMEs annually by 2020.

Strengthen our early-stage pipeline through novel science and technology.

Transform our innovation and culture model
Focus on novel science, such as immune-mediated therapy combinations and precision medicine.

Co-location near bioscience clusters at three strategic centres in Cambridge, UK; Gaithersburg, MD, US; and Gothenburg, Sweden helps to leverage our capabilities and foster collaboration with leading scientists and research organisations.

Accelerate through business development
Work to reinforce our therapy areas and strengthen our portfolio and pipeline through targeted business development, including collaborations, in-licensing and acquisitions.

Collaborate strategically to broaden and accelerate the development of pipeline assets (externalisation) and divest non-core assets to realise value.

NME Phase II starts/progressions

9

2018	**9**
2017	14
2016	16[1]

[1] 15 for determining annual bonus.
See from page 127.

Phase III investment decisions

19

2018	**19**
2017	9
2016	7

NME or LCM project regulatory submissions in major markets

28

2018	**28[1]**
2017	18[2]
2016	14[3]

[1] 24 for determining annual bonus.
[2] 13 for determining annual bonus.
[3] 13 for determining annual bonus.
See from page 127.

NME and major LCM regional approvals

23

2018	**23**
2017	19
2016	11

Note: The Clinical-stage strategic transactions KPI, covering acquisition, licensing and divestment deals, has been removed from Achieve Scientific Leadership. The impact of this activity is captured in the Group financial targets which better reflects the results, rather than a separate measure for the number of deals.

Achieve Scientific Leadership from page 25;
Therapy Area Review from page 50;
Development Pipeline from page 212.

"We delivered three new molecular entities (NMEs) in 2018 and are on target to meet our goal of sustainably delivering two NMEs annually by 2020."

Strategic priorities

Key Performance Indicators

Return to Growth

Focus on Growth Platforms

Emerging Markets – Focus on delivering innovative medicines by investing in Emerging Markets' capabilities, with a focus on China and other leading markets, such as Brazil and Russia. The ongoing transformation of our capabilities is supporting new medicines and improving access and affordability.

Respiratory – Work to maximise pipeline value, devices and medicines to fulfil unmet medical need and improve patient outcomes in asthma and COPD. Includes all respiratory brands.

New CVRM – Since 2017, New CVRM Growth Platform includes *Brilinta*, *Onglyza* franchise (*Onglyza* and *Kombiglyze*), *Farxiga* franchise (*Farxiga* and *Xigduo*), Exenatide Total (*Byetta* and *Bydureon*), *Symlin*, *Qtern*, roxadustat, *Epanova* and *Lokelma*.

Japan – Strengthen our Oncology franchise and work to maximise the success of our Diabetes medicines.

Oncology – Aim to deliver six new cancer medicines to patients by 2020. Since 2014, we have delivered five Oncology medicines to date: *Lynparza*, *Tagrisso*, *Imfinzi*, *Calquence* and *Lumoxiti* that make a meaningful difference to patients.

Transform through specialty care, devices and biologics

Biologic medicines now account for about half of our NMEs in development, potentially enhancing asset longevity. A greater focus on innovative and differentiated delivery devices affords patients choice while ensuring product durability. Our new specialty care portfolio is expected to balance our strength in primary care medicines.

Emerging Markets

$6,891m
Product Sales

2018	**$6,891m**
2017	$6,149m
2016	$5,794m

Actual growth	CER growth
2018 +12%	2018 +13%
2017 +6%	2017 +8%
2016 0%	2016 +6%

Respiratory

$4,911m
Product Sales

2018	**$4,911m**
2017	$4,706m
2016	$4,753m

Actual growth	CER growth
2018 +4%	2018 +3%
2017 -1%	2017 -1%
2016 -5%	2016 -3%

New CVRM

$4,004m
Product Sales

2018	**$4,004m**
2017	$3,567m
2016	$3,266m

Actual growth	CER growth
2018 +12%	2018 +12%
2017 +9%	2017 +9%
2016 +15%	2016 +17%

Japan

$2,004m
Product Sales

2018	**$2,004m**
2017	$2,208m
2016	$2,184m

Actual growth	CER growth
2018 -9%	2018 -11%
2017 +1%	2017 +4%
2016 +8%	2016 -3%

Oncology[2]

$6,028m
Product Sales

2018	**$6,028m**
2017	$4,024m
2016	$3,383m

Actual growth	CER growth
2018 +50%	2018 +49%
2017 +19%	2017 +19%
2016 +20%	2016 -20%

[1] Total removes the effect of certain Product Sales which are included in more than one Growth Platform. Reconciliation to the number used for calculating annual bonus is shown from page 127.

[2] In 2018, Oncology Growth Platform included the entire Oncology portfolio. Prior years have been revised on this basis.

Return to Growth from page 29; Therapy Area Review from page 50.

$18,464m

Revenue from Growth Platforms of $18,464 million[1] in 2018 represented 84% of Total Revenue

Key Performance Indicators *continued*

Strategic priorities | Key Performance Indicators

Be a Great Place to Work*

Evolve our culture
Improve our employees' engagement with our Purpose and Values and promote greater understanding of, and belief in, our strategy.

Simplify our business
Develop simpler, more efficient processes and flatten our organisational structure to improve productivity, encourage accountability and improve decision making and communication.

Attract and retain the best talent
An inclusive environment that enhances our ability to attract and retain diverse talent with critical capabilities.

Be a Great Place to Work from page 38.

Employee belief in our strategy

89%

2018	89%[1]
2017	88%[2]
2016	80%[3]

[1] Source: December 2018 Pulse survey across a sample of the organisation.
[2] Source: December 2017 Pulse survey across a sample of the organisation.
[3] Source: December 2016 Pulse survey across a sample of the organisation.

Organisational structure – % of employees within six management steps of the CEO

72%

2018	72%
2017	70%
2016	82%

Employees who would recommend AstraZeneca as a great place to work

83%

2018	83%[1]
2017	81%[2]
2016	74%[3]

[1] Source: December 2018 Pulse survey across a sample of the organisation.
[2] Source: December 2017 Pulse survey across a sample of the organisation.
[3] Source: December 2016 Pulse survey across a sample of the organisation.

Do business sustainably†

Making science accessible
Deliver our business strategy in a way that brings wider benefits to society and the planet.

Focus on:

> increasing access to healthcare for more people
> furthering ethics and transparency in everything we do
> reducing environmental impacts on human health and the natural world.

Connect our work with the UN Sustainable Development Goals and integrate our commitments into day-to-day business activities.

Sustainability from page 42.

Ethics: Non-compliance with our Code of Ethics

56.6
per 1,000 employees in Commercial Regions

2018	56.6
2017	41.4
2016	50.7

There were 2,042 instances, most of them minor, of non-compliance with our Code of Ethics or supporting requirements in our Commercial Regions by employees and third parties.

Health: Reaching people through our Access to Healthcare programmes

12.0m
people

2018	12.0m
2017	7.2m
2016	4.2m

Our Access to Healthcare programmes, including Healthy Heart Africa, Healthy Lung, and Phakamisa, have reached 12.0 million people through education, screenings, diagnosis and treatment cumulatively since the start of each programme.

Environmental protection: Operational greenhouse gas (GHG) footprint[1]

1,769 kt CO_2e

2018	1,769 kt CO_2e
2017	1,705 kt CO_2e
2016	1,684 kt CO_2e

[1] Operational GHG footprint is emissions from all Scope 1, 2 and selected Scope 3 sources. See page 231.

Our 2018 operational GHG footprint met our target of progressing our Science Based Targets and represents a 0.4% reduction from our 2015 baseline.

* We will review the Be a Great Place to Work KPIs in 2019 to evaluate appropriate representation of the strategy. Where possible, we will continue to make updates on current indicators publicly available.

† As disclosed in the 2017 Annual Report, we reassessed our Do business sustainably KPIs in 2018:

> We added an Ethics & Transparency KPI to measure progress for our third sustainability focus area.
> We expanded the Access to Healthcare KPI to incorporate more of our programmes.
> We changed the title of our Environmental protection KPI. In line with World Resources Institute GHG Protocol, a carbon dioxide equivalent (CO_2e) number can be used to report on GHGs, and it is commonly called 'carbon'. At AstraZeneca, the majority of our operational GHG footprint is from non-CO_2 GHGs so we are now using the better representation of 'GHG'. There is no change in the content of our CO_2e reporting.
> The retired KPIs are reported for continuity in the 2018 Sustainability Report on www.astrazeneca.com/sustainability. The retired KPIs are the Dow Jones Sustainability Index rating and number of people reached through only our Healthy Heart Africa programme.

"Our achievements are only made possible by a skilled and talented team who live our Values and are true to our Purpose."

Strategic priorities | Key Performance Indicators

Achieve Group Financial Targets

Cost discipline
Our aim is to deliver great medicines for patients while maintaining cost discipline and a flexible cost base.

Maintain a progressive dividend
Policy is to maintain or grow dividend per share.

Maintain a strong balance sheet
Target a strong, investment-grade credit rating and optimal cash generation.

Product Sales[1,2]

$21,049m

Actual growth	CER growth
2018 +4%	2018 +4%
2017 -5%	2017 -5%
2016 -10%	2016 -8%

// Denotes a scale break.

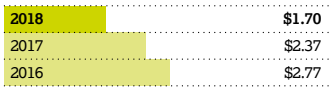
Net cash flow from operating activities[2]

$2,618m

Actual growth
2018 -27%
2017 -14%
2016 +25%

Reported EPS

$1.70



Actual growth	CER growth
2018 -28%	2018 -29%
2017 -14%	2017 -15%
2016 +24%	2016 +9%

Core EPS[2]

$3.46

Actual growth	CER growth
2018 -19%	2018 -19%
2017 -1%	2017 -2%
2016 +1%	2016 -5%

Dividend per share[3]

$2.80

"The Board reaffirms its commitment to the progressive dividend policy."

[1] The Total Revenue KPI has been replaced by Product Sales which aligns with our external guidance and focus on commercial execution to drive Product Sales growth. Product Sales and Externalisation Revenue make up Total Revenue.
[2] Reconciliation to the number used for calculating annual bonus is shown from page 127.
[3] First and second interim dividend for the year.

Financial Review from page 74.

The first phase in AstraZeneca's strategy focused on strengthening and accelerating our pipeline. In the second phase, it was on driving our Growth Platforms and launching new products. Following our return to Product Sales growth, our focus is now on delivering sustainable growth through innovation.

In this Business Review, we report on how the elements of our business are delivering against our strategic priorities which are to:

1. Achieve Scientific Leadership
2. Return to Growth
3. Be a Great Place to Work

Our operating model includes our Research & Development (R&D), Commercial and Operations functions, together with our Enabling Units. It is outlined below.

In January 2019, we announced organisational changes to support continued scientific innovation and commercial success as we enter the next phase in our strategic development. The changes are designed to further integrate R&D and accelerate decision making and the launches of new medicines, consolidating what we believe is already one of the most exciting and productive pipelines in the industry.

We are also enhancing our commercial functions to increase collaboration with our R&D organisation, enabling greater commitment to our main therapy areas. We want AstraZeneca to be more agile, collaborative and focused on bringing innovative medicines to patients.

The functions will share many common areas, including basic biology and science platforms as well as medicine supply, manufacturing and IT infrastructure to improve efficiency. These resources will continue to be allocated on a Group-wide basis, according to the overall therapy-area considerations and strategy.

Since 2007, we have made significant efforts to restructure and reshape our business to control costs and improve long-term competitiveness.

Full details are provided in the Financial Review from page 74.

Research & Development

Our R&D activities focus on three strategic R&D centres: Gaithersburg, MD, US; Gothenburg, Sweden; and Cambridge, UK, which is also our global HQ.

In 2018, we managed our R&D activities with two discovery and early-stage biotech units (Innovative Medicines and Early Development, and MedImmune) and one late-stage development unit (Global Medicines Development – GMD).

From January 2019, we are creating therapy area-focused R&D units that are responsible for discovery through to late-stage development – one for BioPharmaceuticals (CVRM and Respiratory) and one for Oncology. This is designed to enable us to follow the science by accelerating promising early-stage assets and life-cycle management programmes, as well as providing new opportunities for combinations.

Operations

Our Operations function plays a key role in development, manufacturing, testing and delivery of our medicines to our customers.

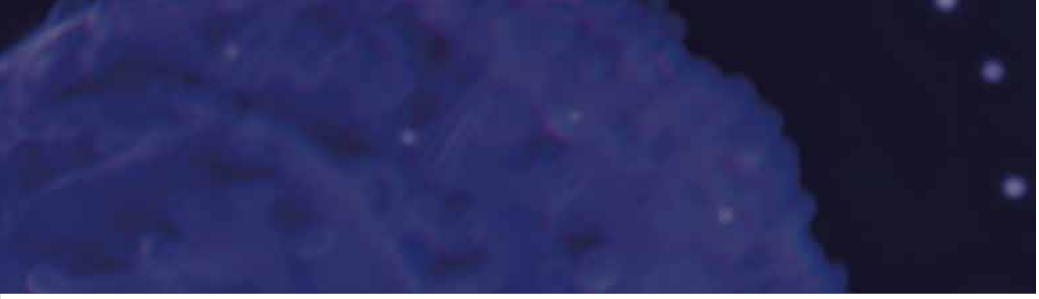
Commercial

In 2018, our sales and marketing functions were grouped into regions: North America (US and Canada); Europe; and International (Emerging Markets, including China, and Australia and New Zealand).

From January 2019, we are creating two commercial units – one for BioPharmaceuticals and one for Oncology. The creation of the BioPharmaceuticals commercial unit aligns product strategy, previously undertaken by our Global Product and Portfolio Strategy group (GPPS), and commercial delivery across CVRM and Respiratory in the US and Europe. These responsibilities mirror the Oncology Business Unit, formed in April 2017, and sharpen our focus on our main therapy areas as we bring new medicines to patients. The International commercial organisation remains unchanged and Japan is categorised separately, being one of our Growth Platforms.

Enabling Units

Finance, Human Resources, Legal, Sustainability, Information Technology.



1. Achieve Scientific Leadership

We are using our distinctive scientific capabilities, as well as investing in key programmes and focused business development, to deliver a pipeline of life-changing medicines.

Overview

During 2018, we had:

> 23 approvals of NMEs or major LCM projects in major markets
  – 13 Oncology approvals for *Imfinzi*, *Lumoxiti*, *Lynparza* and *Tagrisso*
  – 6 CVRM approvals for *Bydureon*, *Bydureon BCise*, *Lokelma* and roxadustat
  – 3 Respiratory approvals for *Bevespi* and *Fasenra*
  – 1 Other approval for *Nexium*
> 28 NME or major LCM regulatory submissions in major markets
> 19 Phase III NME investment decisions
> 9 Phase II starts
> Accelerated reviews included
  – 1 Breakthrough Therapy designation
  – 3 Orphan Drug designations
  – 3 Priority Review designations
> 18 projects discontinued

Scientific leadership and collaboration

AstraZeneca's Purpose is to push the boundaries of science to deliver life-changing medicines. It underpins everything we do. However, as we seek to achieve scientific leadership, we know that we cannot do so alone. We want the way we work to be inclusive, open and collaborative. We believe our operating model gives us access to the best science, both internal and external, and we are open to exploring new and different kinds of collaborations.

One of the measures of our success in achieving scientific leadership and demonstrating the quality of research conducted in our laboratories is the number of publications in high-quality and 'high-impact' journals. It is also critical for recruiting and retaining the best scientists from around the world. Scientists from IMED, MedImmune and GMD have published 102 manuscripts (up by 20 compared with 2017, a record number) in 'high-impact' peer-reviewed journals, each with an impact factor exceeding 15 (Thomson Reuters 5yr IF score) and a score exceeding 955 in total. This represents a fourteen-fold improvement since 2012.

Early science

During 2018, both IMED and MedImmune worked to strengthen our early-stage product portfolio by exploring novel biology across our disease areas and developing the best molecules to address unmet medical need. The diversity of technologies applied in our early pipeline is exemplified by the increased number of new modalities entering clinical development: 12 in 2018 compared to six in 2012. For example, our collaboration with Moderna is exploring the use of modified ribonucleic acid (mRNA) for cardiac regeneration in patients undergoing coronary artery bypass graft surgery (AZD8601) as well as an additional programme where we are evaluating anti-cancer T cell responses with mRNA therapies in patients with solid tumours. With Ionis Pharmaceuticals, Inc., we are investigating an antisense oligonucleotide in immuno-oncology (danvatersin), in combination with *Imfinzi*. With Pieris Pharmaceuticals, AZD1402 entered clinical development in 2018 as a novel inhaled drug for asthma based on its proprietary bicyclic peptide platform. In addition, we continue evaluation of our DNA-based cancer vaccine targeting HPV-16 and HPV-18 (MEDI0457) in collaboration with Inovio Pharmaceuticals, Inc.

Since 2014, we have had 26 diagnostic tests approved in the US, EU and Japan. They support four precision medicines for patients with some of the most challenging diseases of our time, including three for lung and ovarian cancers: therapies that target the epidermal growth factor receptor (EGFR), including the T790M resistance mutation; the poly ADP ribose polymerase (PARP) pathway; and the programmed death-ligand (PD-L1) pathway. Approximately 90% of our pipeline now has a precision medicine approach and reflects the broad range of cutting-edge technologies, tissue diagnostics, next-generation sequencing and point of care diagnostics we have introduced.

For more information, see Therapy Area Review from page 50.

Transforming medical science

We are determined to advance our understanding of disease biology to uncover novel drivers for the diseases we aim to treat, prevent, and even cure. We aim to foster an environment where our scientists can freely share their ideas and collaborate with the best external partners. Our approach to science is exemplified by the number of joint research facilities we have established with leading scientific centres, such as the Karolinska Institutet in Sweden and the CRUK Cancer Institute in Cambridge. In 2018, we extended our joint research facility at the Max Planck Institute to include the Chemical Genomics Centre III, focused on novel basic research in the biosciences and chemical biology. With the Swedish Innovation Bridge Company (SWIBCo), we established a partnership with Procella Therapeutics and Smartwise to develop novel stem cell-based therapies for heart failure. The Blue-Sky fund we established with the MRC Laboratory of Molecular Biology (LMB) is now in its fourth year of funding projects which involve 40% of LMB's Principal Investigators. A recent project breakthrough uncovered the first protein structures for human ataxia telangiectasia mutated (ATM), a key trigger protein in the DNA damage response (DDR) and a prime therapeutic target in cancer. In 2018, we announced a collaboration to develop and commercialise a gene therapeutic for patients with chronic lung disease, utilising 4D Molecular Therapeutics' novel discovery platform to generate optimised adeno-associated virus (AAV) vectors. We also continue to advance our strategic research collaboration with Ethris GmbH where we are evaluating mRNA-based therapies in pulmonary diseases.

Innovating in drug discovery

We are also exploring emerging technologies to accelerate the design and testing of tomorrow's medicines. For example, artificial intelligence (AI) is being used increasingly in the pharmaceutical sector building on the emergence of novel computing technologies, the exponential increase in data and deep learning algorithms. Our teams are looking across the discovery and development process, from target identification to clinical trials, to understand where we can harness new technologies and further automate processes, freeing up more time for discovering and delivering as many new medicine programmes as we can from our pipeline. In Drug Discovery, our teams are facilitating rapid, unbiased drug design and speeding up compound synthesis through improvements in AI algorithmic processes. In the previous two years, our scientists have published more than 20 scientific publications showing improvements in algorithmic processes in drug design. We are also collaborating with the University of Bern and University of Bonn in ExCAPE, an EC-funded project that harvests the power of supercomputers to speed up drug discovery using machine learning. Through the acquisition of Definiens in 2014, we are

developing new AI approaches to evaluate complex morphology, such as in the tumour microenvironment. In Early Development, we are starting to connect high-density datasets, from imaging, biosensors, multiomics and quality-of-life information, to inform earlier decision making in clinical trials. In a recent publication in *Lancet Respiratory Medicine*, we describe a novel modelling tool that has the potential to reduce the time of Phase II trials in respiratory by half.

Late-stage development

During 2018, GMD delivered clinical trial data and submissions that resulted in 23 approvals for new medicines in the US, EU, China and Japan. As shown in the table opposite, our pipeline includes 149 projects, of which 131 are in the clinical phase of development, and we are making significant progress in advancing our late-stage programmes through regulatory approval with 28 NME or major LCM regulatory submissions during 2018.

At the end of the year, we had eight NME projects in pivotal studies or under regulatory review (covering 15 indications), compared with 11 at the end of 2017.

Also in 2018, 20 NMEs progressed to their next phase of development and 18 projects were discontinued: 15 for poorer than anticipated safety and efficacy results; and three as a result of a strategic shift in the environment or portfolio prioritisation.

As is to be expected when we are investigating treatments for diseases that are hard to treat, we also had some setbacks during the year. These included disappointing Phase III data results. For example, the results of the MYSTIC trial showed that *Imfinzi* in combination with tremelimumab for 1st line non-small cell lung cancer (NSCLC) did not meet the primary endpoint of overall survival (OS), and the Phase III EAGLE trial of *Imfinzi* and tremelimumab did not meet the primary endpoints of improving OS in advanced head and neck cancer relative to standard of care chemotherapy. Along with Lilly, we also discontinued development of lanabecestat for Alzheimer's disease after an independent data monitoring committee concluded that the trials were unlikely to meet their primary endpoints and recommended the trials be stopped for futility.

Accelerating the pipeline

GMD is prioritising its investment in specific programmes to accelerate them so that new treatments get to patients more quickly but still safely. As a result, we had numerous study read-outs in 2018, including *Lynparza* in 1st line BRCA-mutated advanced ovarian cancer (SOLO-1), *Imfinzi* OS results in unresectable stage 3 NSCLC, the *Farxiga* cardiovascular outcomes trial in adults with type-2 diabetes (DECLARE) and the *Fasenra* Phase III extension trial evaluating long-term safety and efficacy (BORA). Our teams have also been quick to turn positive clinical trial data into regulatory submissions. In 2018, we made submissions in the US, EU, Japan and China for *Lynparza* for 1st line maintenance treatment for advanced BRCA-mutated ovarian cancer, and *Bevespi* for Chronic Obstructive Pulmonary Diseases (COPD) in the EU, Japan and China. We also received approval in the US and EU for *Lokelma* for the treatment of adults with hyperkalaemia, *Lumoxiti* in the US for the treatment of adults with relapsed or refractory hairy cell leukaemia (HCL), roxadustat for the treatment of anaemia in Chronic Kidney Disease (CKD) in China, *Fasenra* for severe asthma in the EU and Japan, and US approval for *Lynparza* for 1st line maintenance treatment for advanced BRCA-mutated ovarian cancer.

In 2018, we presented scientific rationale that resulted in four regulatory designations for Breakthrough Therapy or Priority Review for new medicines which offer the potential to address unmet medical need in certain diseases, including tezepelumab in patients with severe asthma, *Lynparza* for ovarian cancer (SOLO-1), *Tagrisso* in 1st line EGFR mutated NSCLC (FLAURA) and *Lumoxiti* in 3rd line HCL (PLAIT). We also secured Orphan Drug designation for the development of three medicines to treat very rare diseases including *Lynparza* for treatment of pancreatic cancer (POLO), selumetinib for the treatment of neurofibromatosis type 1 (SPRINT) and *Fasenra* for the treatment of eosinophilic granulomatosis with polyangitis (EGPA).

We also collaborate to advance our clinical research – from strategic alliances with contract research organisations (CROs) for the delivery of clinical trials, to academic collaborations.

Life-cycle management

We also drive an extensive life-cycle management programme for already-approved medicines to pursue further indications and label updates to expand the potential for our products to help more patients. For example, this year we made regulatory submissions for *Lynparza* in the EU to extend treatment into breast cancer; *Farxiga* for type-1 diabetes in the US, EU and Japan; and saxagliptin + dapagliflozin + metformin for type-2 diabetes in the US and EU. We also secured approvals for important life-cycle programmes such as *Imfinzi* in the US, EU and Japan for 1st line treatment of stage 3 NSCLC; *Lynparza* for BRCA-mutated metastatic breast cancer in the US and Japan; *Lynparza* for platinum-sensitive relapsed ovarian cancer in the EU, China and Japan; *Tagrisso* for 1st line treatment of EGFR mutated NSCLC; and *Bydureon BCise*, a new formulation of once-weekly *Bydureon* in a single-dose, pen-filled device.

R&D resources

We have approximately 8,900 employees in our R&D organisation, working in various sites around the world. We have three strategic R&D centres: Cambridge, UK; Gaithersburg, MD, US; and Gothenburg, Sweden. Other R&D centres are located in the UK (Alderley Park and Macclesfield), the US (Waltham, MA and California), Japan (Osaka) and China (Shanghai). We also have a site in Poland (Warsaw) that focuses on late-stage development.

In 2018, R&D expenditure was $5,932 million (2017: $5,757 million; 2016: $5,890 million), including Core R&D costs of $5,266 million (2017: $5,412 million; 2016: $5,631 million). In addition, we spent $476 million on acquiring product rights (such as in-licensing) (2017: $404 million; 2016: $821 million). We also invested $94 million on the implementation of our R&D restructuring strategy (2017: $201 million; 2016: $178 million). The allocations of spend by early-stage and late-stage development are presented in the R&D spend analysis table below.

R&D spend analysis

	2018	2017	2016
Discovery and early-stage development	**37%**	36%	36%
Late-stage development	**63%**	64%	64%

Development pipeline overview (as at 31 December 2018)

Phase I 38

> 38 projects in Phase I, including:
- 26 NMEs
- 12 oncology combination projects

Phase II 43

> 43 projects in Phase II, including:
- 25 NMEs
- 6 significant additional indications for projects that have reached Phase III
- 12 oncology combination projects

Late-stage development* 22

> 22 projects in late-stage development, either in Phase III/ pivotal Phase II studies or under regulatory review:
- 8 NMEs not yet approved in any market
- 7 projects exploring additional indications for these NMEs
- 7 NMEs already approved or launched in the EU, China, Japan and/or the US

* NMEs and significant additional indications.

Life-cycle management projects* 46

> 46 LCM projects*

* Only includes material projects where first indication is launched in all markets.

Cambridge

Cambridge, UK, is a world-leading academic and life sciences hub, and is where we are building our new strategic R&D centre and global corporate headquarters. With around 2,500 AstraZeneca and MedImmune staff now located in the city, we are already seeing the impact of significant scientific and strategic collaborations within the Cambridge cluster.

Construction began in April 2015 and during 2018, the focus of our activities at the site on the Cambridge Biomedical Campus (CBC) shifted from the base building infrastructure and exterior towards the fit-out of laboratory and scientific support spaces, interior design of the office areas and landscaping. Reflecting this shift of focus, we changed construction manager with effect from November 2018.

We remain committed to the design principles of the site and making it a great place to work. The complexity of the building project is reflected in the updated schedule, in which we are expected to start occupation of the building from 2020 rather than have it fully operational in that year as reported in our previous Annual Report. We believe that with our staff in Cambridge already delivering the strategic goals around our decision to locate ourselves in the city, we do not need to press for earlier occupation by adjusting the building programme.

Costs for the project have risen since our original cost projection due to the complexity of the build, construction cost inflation, including the impact of a weakening pound sterling, and increased investment in new technologies and equipment (for example genomics, screening lab) as part of our ongoing investment in R&D in the UK. The new construction manager is reviewing cost estimates but our current cost projection for the project is in the region of £750 million. The project is being funded out of operational cash flows.

Our longer-term vision is to have our non-laboratory-based Cambridge colleagues co-located on the CBC and near our key scientific, research and clinical partners. We are now updating the overall master plan for the site and the next stage will be the development of an office building opposite our R&D centre that can accommodate an additional 1,000 people.

8,900

We have approximately 8,900 employees in our R&D organisation

$5.9bn

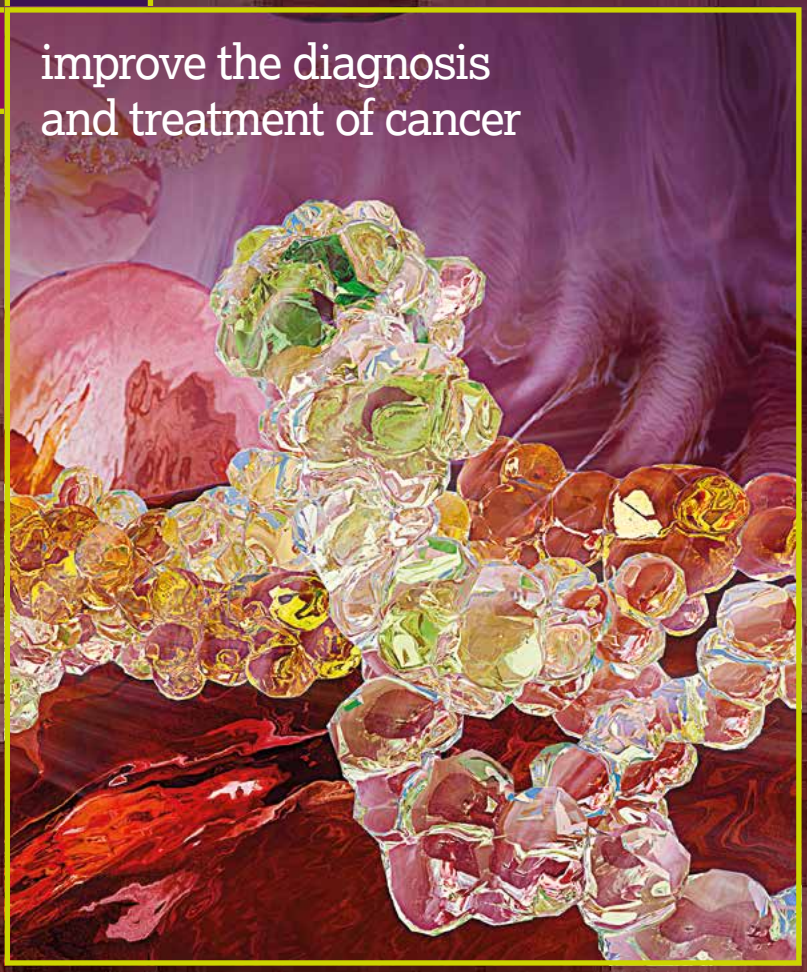
$5,932 million invested in our science

"AstraZeneca is partnering with world-leading diagnostic developers to deliver complete disease profiling with a single ctDNA test continuing to improve outcomes for patients."

can

Science

improve the diagnosis and treatment of cancer



30%

Some 30% of biopsies can 'fail'

AstraZeneca has pioneered the use of circulating tumour DNA (ctDNA) for the detection of biomarkers in cancer. Pieces of DNA are shed from a tumour and circulate in the bloodstream where they can be analysed to give genetic information about a patient's tumour. The world's first ctDNA diagnostic test was associated with *Iressa* for specific mutations in the epidermal growth factor receptor (EGFR), namely Exon 19 deletions and L858R in patients with non-small cell lung cancer. It is an approach that allows healthcare professionals to determine the right treatment for a patient using a minimally invasive blood test in place of a biopsy, a more invasive method that can 'fail' in some 30% of cases. AstraZeneca is partnering with world-leading diagnostic developers to deliver complete disease profiling with a single ctDNA test continuing to improve outcomes for patients.

Circulating tumour DNA also has an important role to play if we are to realise our ambition of eliminating cancer as a cause of death. We believe it has the potential to improve drug development by identifying patients who are at risk of relapse and enabling rapid changes in therapy to address this. For example, in early-stage lung cancer, the majority of patients are cured by surgery and chemoradiation therapy. The key to improving overall survival in these stages is to identify those patients at high risk of early relapse and an emerging potential way to do this is by detecting the failure to clear ctDNA from the blood once curative intent treatment has been completed. Investigating the clinical utility and validity of ctDNA in this setting is an active area of research. For example, for these high risk patients, we can test in a minimally invasive manner whether three months' intervention with investigational compounds removes residual disease as evidenced by the clearance of ctDNA, and whether this ultimately impacts long-term outcomes.

Circulating tumour DNA – see caption on inside front cover.

2. Return to Growth

Our return to Product Sales growth was underpinned by our focus on our Growth Platforms and leveraging our strong global commercial presence, particularly in Emerging Markets, to ensure the right medicines are available and that patients have access to them.

Overview

> Product Sales of $21,049 million (up 4% at actual rate of exchange; 4% at CER) and Externalisation Revenue of $1,041 million (down 55%; 55% at CER), resulting in Total Revenue of $22,090 million (down 2%; 2% at CER)

> Growth Platforms revenue of $18,464 million, up 13% (12% at CER)
  - Emerging Markets: Sales growth of 12% (13% at CER) to $6,891 million. China sales in the year grew by 28% (25% at CER), supported by the launches of new medicines
  - Respiratory: Sales grew by 4% (3% at CER). *Symbicort* sales declined by 9% (10% at CER), *Pulmicort* sales rose by 9% (8% at CER) and *Fasenra* performed well in the countries where it had been launched
  - New CVRM: Sales growth of 12% (12% at CER). Strong performances from *Farxiga* and *Brilinta*, with sales of each exceeding $1.3 billion in 2018
  - Japan: Sales decline of 9% (11% at CER). The impact of generic *Crestor* was felt faster than expected and the biennial price reduction also impacted sales
  - Oncology: Sales growth of 50% (49% at CER). Sales of *Tagrisso* reached $1,860 million to become AstraZeneca's largest-selling Oncology medicine

> US revenue was up by 11% to $6,876 million; Europe was down by 6% (10% at CER) to $4,459 million; and Established ROW was down by 8% (9% at CER) to $2,823 million

> 81% increase in New Medicines[1] revenue (81% at CER), contributing 30% of Total Revenue

[1] *Tagrisso, Imfinzi, Lynparza, Calquence, Lumoxiti, Brilinta, Farxiga, Lokelma, Bevespi* and *Fasenra.*

Our plans for growth

Our Commercial teams, which comprised around 36,100 employees at the end of 2018, are active in more than 100 countries. In most countries, we sell our medicines through wholly-owned local marketing companies. We also sell through distributors and local representative offices. We market our products largely to primary care and specialty care physicians.

Our return to Product Sales growth was underpinned by our Growth Platforms. As shown on page 21 and above, these comprise our three main therapy areas, together with Emerging Markets and Japan. In 2018 they grew by 13% (12% at CER) and represent 84% of Total Revenue.

Sales of our New Medicines[1] generated incremental sales of $2.8 billion at CER and represented 30% of Total Revenue. These New Medicines are important platforms for future growth. In Emerging Markets, they represented 15% of sales, up from 10% in 2017 and, in the US, they represented 48% of Product Sales, up from 26%. US performance reflected, in particular, the success of the new Oncology medicines plus the strong performance of *Fasenra*. In Europe, the decline in Product Sales reflected the impact of generic *Crestor* medicines in various markets in 2017 and continued competitive and price pressures. New Medicines represented 28% of Product Sales, up from 18% in 2017. In Established Rest of World, New Medicines represented 24% of sales in the year, up from 13% in 2017.

However, the pharmaceutical market is highly competitive. For example, our Diabetes franchise continues to see pricing pressure. In immuno-oncology, the large number of clinical trials that are being carried out highlight the competitive nature of this area and renders speed to market critical.

Regional Product Sales

1. Emerging Markets
12%
12% growth in the year (13% at CER) to $6,891m

2. US
11%
11% growth in the year (11% at CER) to $6,876m

3. Europe
(6)%
6% decline in the year (10% at CER) to $4,459m

4. Established Rest of World
(8)%
8% decline in the year (9% at CER) to $2,823m

All numbers as at 31 December 2018.

Pricing and delivering value

Our medicines help treat unmet medical need, improve health and create economic benefits. Effective treatments can lower healthcare costs by reducing the need for more expensive care, preventing more serious and costly diseases and increasing productivity. We are committed to a pricing policy for our medicines based on four principles:

> We determine the price of our medicines while considering their full **value** for patients, payers and society. The agreement on price involves many national, regional and local stakeholders, reflecting factors such as clinical benefit, cost effectiveness, improvement to life expectancy and quality of life.

> We aim to ensure the **sustainability** of both the healthcare system and our research-led business model. We believe we share a collective responsibility with healthcare providers and other stakeholders to work together to enable an efficient healthcare system for patients today and support a pipeline of new medicines for patients tomorrow.

> We seek to ensure appropriate patient **access** to our medicines. We work closely with payers and providers to understand their priorities and requirements, and play a leading role in projects to align better the requirements of regulatory and health technology assessment (HTA) agencies or other organisations that provide value assessment of medicines. For example, we have a leading role in the European IMI ADAPT-SMART programme for exploring adaptive licensing.

> We pursue a **flexible** pricing approach that reflects the wide variation in global healthcare systems. We have developed patient access programmes that are aligned with the ability to pay of patients and healthcare systems. We are committed to the appropriate use of managed entry schemes and the development of real-world evidence and we are investigating innovative approaches to the pricing of medicines, such as payment for outcomes received by the patient and healthcare system.

By way of example of our approach, we apply Tiered Pricing Principles globally. This defines price levels commensurate with affordability based on a country's ability to pay. We believe that this approach to pricing is sustainable and fair, and that it will increase access and improve patient outcomes in Emerging Markets.

More generally, we remain committed to exploring innovative solutions to improve patient access and affordability, focusing on the value our medicines bring to patients and the healthcare system. We are collaborating with payers to conclude value-based pricing solutions that improve patient outcomes and have entered into 37 such agreements across our therapy areas. For more information, see the case study on page 17.

US

As the sixteenth largest prescription-based pharmaceutical company in the US, we have a 2.5% market share of US pharmaceuticals by sales value. In 2018, Product Sales in the US increased by 11% to $6,876 million (2017: $6,169 million).

The US healthcare system is complex with multiple payers and intermediaries exerting pressure on patient access to branded medicines through regulatory and voluntary rebates. Regulatory rebates are statutorily mandated chargebacks and discounts paid on government-funded programmes such as Medicaid, Department of Defense (including TRICARE) and Department of Veteran's Affairs. Voluntary rebates are paid to managed care organisations and pharmacy benefit managers for commercially insured patients, including Medicare Part D patients. In the Medicare Part D programme, in addition to voluntary negotiated rebates, branded pharmaceutical manufacturers are statutorily required to pay a percentage of the patient's out-of-pocket costs during the 'coverage gap' portion of their benefit design. From the beginning of 2019, the mandatory coverage gap discount increased to 70% from its former amount of 50%, as a result of the passage of legislation in 2018. As part of the Affordable Care Act (ACA), we also pay a portion of an overall industry Patient Protection and Affordable Care Act Branded Prescription Drug Fee.

In 2018, the overall measurable reduction in our profit before tax for the year due to discounts on branded pharmaceuticals in the Medicare Part D Coverage Gap and an industry-wide HealthCare Reform Fee was $432 million (2017: $119 million; 2016: $471 million).

In the US, there is significant pricing pressure driven by payer consolidation, restrictive reimbursement policies and cost control tools, such as exclusionary formularies and price protection clauses. Many formularies, which specify particular medicines that are approved to be prescribed in a healthcare system, or under a health insurance policy, employ 'generic first' strategies and/or require physicians to obtain prior approval for the use of a branded medicine where a generic alternative exists. These mechanisms can be used by intermediaries to limit the use of branded products and put pressure on manufacturers to reduce net prices. In 2018, 84.8% of prescriptions dispensed in the US were generic, compared with 84.9% in 2017. In addition, patients are seeing changes in the design of their health plan benefits and may experience variation, including increases, in both premiums and out-of-pocket payments for their branded medications. The patient out-of-pocket spend is generally in the form of a co-payment or co-insurance, but there is a growing trend towards high-deductible health plans which require patients to pay the full list price until they meet certain out-of-pocket thresholds.

Ongoing scrutiny of the US pharmaceutical industry, focused largely on pricing, has been the basis of multiple policy proposals in the US. In May 2018, the Trump Administration issued its 'Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs', which included a wide range of policy proposals that would impact the US pharmaceutical industry if implemented. Proposed changes under consideration include, but are not limited to, fundamentally changing the role of rebates in the pharmaceutical supply chain, reforms to the 340B Drug Pricing Program, and policies to increase competition in the Medicare programme and encourage generic drug use. The Trump Administration has already taken action on several of the policies discussed in the Blueprint, and more policy actions are pending. In addition, lawmakers at both the federal and state level have sought increased drug pricing transparency and have proposed and implemented policies that include measures relating to the submission of proprietary manufacturer data, establishment of price parameters that are indexed to certain federal programmes, and reporting of changes in pricing beyond certain thresholds.

Though widespread adoption of a broad national price control scheme in the near future is unlikely, we continue to comply with new state-level regulations in this area and we recognise the sustained potential for substantial changes to laws and regulations regarding drug pricing that could have a significant impact on the pharmaceutical industry.

We understand that our medicines will not benefit patients if they are unable to afford them and that is why we offer a number of resources and programmes that can help increase patients' access to medication and reduce their out-of-pocket costs. We focus our formulary access on affordability for patients through rebate payments as well as savings cards for eligible patients when the out-of-pocket costs are not affordable. AstraZeneca has one of the longest-standing patient assistance programmes in the industry, AZ&Me, which provides eligible patients with AstraZeneca medicines at no cost. AstraZeneca has provided prescription savings to four million patients across the US and Puerto Rico over the past 10 years.

For more information, see Community investment on page 48.

Europe

The total European pharmaceutical market was worth $196 billion in 2018. We are the fifteenth largest prescription-based pharmaceutical company in Europe (see Market definitions on page 239) with a 2.0% market share of pharmaceutical sales by value.

In 2018, our Product Sales in Europe decreased by 6% at actual rate of exchange (10% at CER) to $4,459 million (2017: $4,753 million). Key drivers of the decline, leaving aside the impact of divestments such as *Seloken*, *Atacand*, *Nexium* and *Zomig*, were continued competition from *Symbicort* analogues, loss of exclusivity for *Crestor*, and the continued impact of early generic entry in certain markets for *Faslodex*, which we expect to continue in 2019. The continued macroeconomic environment, pricing pressure from payers and parallel trade across markets also affected sales.

Despite these conditions, we continued to launch innovative medicines across Europe and saw encouraging performance for certain products across our Growth Platforms, in particular with *Forxiga*, *Brilinta*, *Fasenra*, *Lynparza* and *Tagrisso*. Oncology sales in Europe grew by 19% (14% at CER), partly driven by the approval of *Tagrisso* for the treatment of patients in the 1st line EGFRm setting in June 2018. *Lynparza* sales grew by 46% (41% at CER), partly benefiting from the approval in May 2018 for its use as a tablet-based treatment for platinum-sensitive ovarian cancer, regardless of BRCA status. *Brilique* sales growth of 18% (13% at CER) was accompanied by *Forxiga* sales growth of 30% (24% at CER). *Fasenra* was successfully launched in several European countries, with a strong initial uptake.

Established Rest of World (ROW)*

In 2018, Product Sales in Japan decreased by 9% at actual rate of exchange (11% at CER) to $2,004 million (2017: $2,208 million), as a result of the biennial government price cuts and increased intervention from the government to rapidly increase the volume share of generic products. In September 2017, a *Crestor* authorised generic entered the market and in December 2017 we saw more than 20 generic companies enter the Japanese statin market with generic rosuvastatin which has strongly impacted *Crestor* Product Sales with a decrease of 60%. Leaving aside these generic restraints, Japan is presenting strong growth from the brands in our Growth Platforms and *Nexium*. In addition, there were particularly strong performances from *Tagrisso*, *Fasenra*, *Imfinzi*, *Lynparza* and the Diabetes franchise. We now hold twelfth position in the ranking of pharmaceutical companies by sales of medicines in Japan. Japan remains an attractive market for innovative pharmaceuticals.

Canada has a mixed public/private payer system for medicines that is funded by the provinces, insurers and individual patients. It has also now become common for public payers to negotiate lower non-transparent prices after they have gone through a review by the Canadian Agency for Drugs and Technology in Health, a health technology assessment body. Most private insurers pay full price, although there is increasing pressure to achieve lower pricing. Overall, the split for AstraZeneca's portfolio is 62% funded by private payers and 38% by public plans.

Our sales in Australia and New Zealand declined by 16% at actual rate of exchange (14% at CER) in 2018. This was primarily due to the continued erosion of *Nexium* and *Seroquel* by generic medicines, further price reductions on established brands and entry of an analogue for *Symbicort* in Australia, which had an impact on both price and volume. Consequently, sales in 2018 declined at a greater rate compared to that seen in 2017. However, the pace of generic erosion has moderated notably with *Crestor* and *Atacand*, while the sales growth from new products such as *Brilinta*, *Lynparza* and the Diabetes portfolio has continued. *Brilinta*, *Lynparza* and the Diabetes portfolio grew by 4% at actual rate of exchange (6% at CER), 41% at actual rate of exchange (43% at CER) and 4% at actual rate of exchange (6% at CER), respectively.

* Established ROW comprises Australia and New Zealand, Canada and Japan.

11%

11% increase in Product Sales in the US in 2018 (11% at CER) to $6,876 million

28%

28% increase in Product Sales in China in 2018 (25% at CER) to $3,795 million

"AstraZeneca was the fastest-growing top 10 multinational pharmaceutical company in Emerging Markets in 2018."

Emerging Markets

Emerging Markets, as defined in Market definitions on page 239, comprise various countries with dynamic, growing economies. As outlined in Marketplace from page 11, these countries represent a major growth opportunity for the pharmaceutical industry due to high unmet medical need and sound economic fundamentals. Emerging Markets are not immune, however, to economic downturn. Market volatility is higher than in Established Markets, and various political and economic challenges exist. These include regulatory and government interventions. In selected markets, governments are encouraging local manufacturing by offering more favourable pricing legislation and pricing is increasingly controlled by governments with price referencing regulations.

Growth drivers for Emerging Markets include new medicines across our Oncology, CVRM and Respiratory portfolios. To educate physicians about our broad portfolio, we are selectively investing in sales capabilities where opportunities from unmet medical need exist. We are also expanding our reach through multi-channel marketing and external partnerships.

With revenues of $6,891 million, AstraZeneca was the fourth largest multinational pharmaceutical company, as measured by prescription sales, and the fastest-growing top 10 multinational pharmaceutical company in Emerging Markets in 2018.

China

In China, AstraZeneca is the second largest pharmaceutical company by value in the hospital sector, as measured by sales. Sales in China in 2018 increased by 28% at actual rate of exchange (25% at CER) to $3,795 million (2017: $2,955 million). We delivered sales growth above the growth rate of the hospital market sector through strategic brand investment, systematic organisational capability improvements and long-term channel expansion programmes in our main therapy areas. In addition, *Tagrisso* was listed in the National Reimbursed Drug List (NRDL) and we launched *Lynparza* during 2018. Pricing practices remain a priority for regulators, and new national regulations, in addition to provincial and hospital tenders, continue to put increasing pricing pressures on pharmaceutical companies in China. In addition, the planned roll-out of the Generics Quality Consistency Evaluation (GQCE) will have an impact on pharmaceuticals budgets and pricing through setting new standards for bioequivalence that generic products must adhere to. The outcome of the latest round of tenders involving *Crestor* and *Iressa* were announced in December 2018 with implementation from early 2019. This is expected to result in a level of sales decline for both brands in 2019. This evaluation is being applied retrospectively, so several existing generic products may fail and be withdrawn which could lead to a consolidation in the sector. This would leave fewer, higher-quality generics in the market thereby putting pressure on any originator brand price premiums and driving a reduction in overall medical costs.

The industry-wide growth rate is expected to be a moderate single digit percentage, following the updates of the NRDL and expanding health insurance coverage. Nevertheless, the healthcare environment in China remains dynamic. Opportunities are arising from incremental healthcare investment, strong underlying demand for our more established medicines and the emergence of innovative medicines such as *Tagrisso* and *Lynparza*.

For more information on our work in China, see page 37.

Emerging market healthcare

We continue to make our medicines affordable to more people on a commercially and socially sustainable basis. As, on average, almost half of medicine funding in emerging countries is paid for by the patient or their families, we base our approach in these markets on an understanding of their economic circumstances and the burden placed on them by health costs. We are aiming to enable our Emerging Markets to deliver better and broader patient access through innovative and targeted equitable pricing strategies and practices.

We have a variety of access programmes around the world, each tailored to meet the needs of the local community, which include a patient's ability to pay. These include patient assistance programmes, such as Terapia Plus in Ukraine, Karta Zdorovia in Russia and FazBem in Brazil. Through these programmes, we help qualifying patients with discounts and donations. We provide these programmes in markets with limited or no public reimbursement system, no coverage beyond the most basic therapies, or where it is unlikely or only after an extended period that public reimbursement is a possible consideration.

AstraZeneca also aims to partner with countries' healthcare systems to optimise access to healthcare. For example, in South Africa, Phakamisa supports the healthcare system by bringing together different organisations to strengthen healthcare capabilities and improve access to treatment and support networks. It aims to reduce the burden of breast and prostate cancer through the promotion of primary prevention and early detection.

In 2017, we launched the Healthy Lung Asia programme, focusing on improving care for asthma, COPD and lung cancer across nine Asian countries (India, Indonesia, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand and Vietnam). The Healthy Lung initiative aims to support: increased awareness; earlier diagnosis; improved treatment; better disease management; and establishing standards of care and initiatives in line with international best practice.

So far, we have initiated 28 formal partnerships and signed 13 memoranda of understanding with national and regional governments, professional organisations and NGOs to drive care improvement, which has enabled Healthy Lung to:

> Support the training of more than 25,000 healthcare professionals.
> Enable diagnosis of more than 500,000 cases of asthma.
> Activate more than 900 Respiratory Centres.
> Align 10 national care guidelines and care pathways to international best practice (GINA).

In 2018, the programme was extended with launches in Latin America, the Middle East and Africa.

Healthy Heart Africa was launched in Kenya in 2014, Ethiopia in 2016 and Tanzania in 2018, supporting the countries to address the burden of NCDs. Since launching, the programme has:

> Conducted 9.97 million blood pressure screenings in the community and in healthcare facilities.
> Trained over 5,800 healthcare workers, including doctors, nurses, community health volunteers and pharmacists, to provide education and awareness, screening and treatment services for hypertension.
> Activated over 700 healthcare facilities in Africa to provide hypertension services, including the establishment of a secure supply chain for low-cost, high-quality antihypertensive medicines.
> Identified over 1.86 million people living with high blood pressure.

In 2018, AstraZeneca began a pilot of clean biogas cooking in Western Kenya. This is enabling the local community to process waste into clean energy, while improving respiratory health of nearby communities by replacing wood-burning fires with alternative fuel sources. The pilot is in partnership with the Cambridge Institute for Sustainability Leadership who will study the environmental impact of this intervention.

For more information on Broadening access to healthcare as one of our sustainability priorities, see page 43.

Operations

Our manufacturing and supply function supports our Return to Growth, and our Operations 2020 plan provides a focus for our investments. They will help ensure we are able to respond to patient and market needs for our medicines.

Operations 2020 was launched in 2015 to enhance supply capabilities in order to respond better to patient and market needs. It focuses on supporting the delivery of our new product launches, strengthening our science and technology capabilities across the globe, creating a more agile and flexible supply chain, and embedding Lean principles throughout our network. Our goal is to be recognised as a leader in the pharmaceutical supply chain by 2020.

Quality, regulation and compliance

We are committed to high product quality, which underpins the safety and efficacy of our medicines. We maintain a comprehensive quality management system to assure compliance and quality. Similarly, we set strict standards for safety, health and environment at each of our sites. Manufacturing facilities and processes are subject to rigorous and continuously evolving regulatory standards. They are subject to inspections by regulatory authorities, who are authorised to mandate improvements to facilities and processes, halt production and impose conditions for production to resume.

To ensure compliance with global Good Manufacturing Practice regulations, the Operations Quality team continuously reviews and strengthens the Quality Systems at our manufacturing sites through internal audit programmes, external intelligence and sharing learnings between sites. In 2018, these measures helped us successfully achieve zero critical observations from 48 independent inspections. We reviewed observations from these inspections together with the outcomes of internal audits and, where necessary, implemented improvement actions.

We are committed to maintaining the highest ethical standards and compliance with internal policies, laws and regulations. We review and comment upon evolving national and international compliance regulations through our membership of industry associations, including IFPMA, EFPIA and PhRMA.

Pharmaceutical Technology & Development

The integration of our Pharmaceutical Technology & Development (PT&D) group into our Operations organisation has been completed, ensuring a seamless transfer of manufacturing technology and processes from our late-stage development group to our commercial manufacturing sites and external partners. PT&D now has a physical presence at our major manufacturing facilities supporting successful product launches, including *Lokelma*, *Bydureon BCise* and *Lynparza* tablets and providing technical leadership for our commercial portfolio throughout the product life-cycle. PT&D is also accountable for the development and introduction of new manufacturing, packaging and analytical technologies across the AstraZeneca small molecule network.

In collaboration with our R&D groups, PT&D is accountable for the development of commercial pharmaceutical products across our pipeline of innovative, small molecule projects. PT&D's core capabilities in chemical development, and oral, inhaled and sterile product development, and digital therapeutics are focused on the development of sustainable processes for medicines designed to meet patients' needs. The clinical operations capability in PT&D works closely with our partners in R&D to design and supply early- and late-stage clinical material and is accountable for the worldwide supply of 260 AstraZeneca sponsored studies.

Supply chain management

We need an uninterrupted supply of high-quality raw materials and active pharmaceutical ingredients (APIs) and, with most of our API manufacturing outsourced, we place great importance on our global external sourcing and procurement organisations and policies, as well as our integrated risk management processes. We purchase materials from a wide range of suppliers and work to mitigate supply risks, such as natural or man-made disasters that disrupt supply chains or the unavailability of raw materials. Contingency plans include using dual or multiple suppliers where appropriate, maintaining adequate stock levels and working to mitigate the effect of pricing fluctuations in raw materials.

As a consequence of the UK's decision to leave the EU, which is anticipated to become effective from 29 March 2019, we have also been working closely with our suppliers on their readiness for the impact this will have, with a view to mitigating the effect on our business.

Since late 2017, we have completed a detailed assessment of approximately 400 suppliers across all areas of our supply chain, including our major and critical suppliers. During 2018, we saw a decline in the overall level of supplier-related risk due to various mitigations, including revised logistics channels, additional warehousing, the potential to move clinical trial related activities, stock building of product and manufacturing related goods, movement of

stock locations, and assessment of the opportunity for supplier substitution. We continue to consider further mitigation activities with a focus on clinical trials and manufacturing given the risk arising from the mix of goods and services, and the associated cross-border UK/EU and EU/UK movements. While we continue to make progress, it is possible that adverse events will impact supplier activities. Issue management may therefore play a key element in our ability to maintain safe supply of our medicines and ongoing business operations more generally.

In addition, as part of our planning to manage the impact of the UK leaving the EU, we have engaged with regulators and government to ensure they have a clear view on the potential impact on pharmaceutical supply chains. We have made significant efforts to duplicate our UK testing capability within the EU and to implement system changes necessary to facilitate compliance with EU law once the UK becomes a third country. Furthermore, we have revised our logistics plans (including shipping routes) and built additional inventory in anticipation of some level of border congestion to reduce the risk of disruption of supply to patients.

Supply chain financing

AstraZeneca has a supply chain finance programme to support the cash flow of its supply base. This programme, in partnership with Taulia Inc. and Greensill Capital, provides suppliers with visibility of invoices and payment dates. Suppliers can access this platform free of charge and have full optionality and flexibility on an invoice by invoice basis to request early payment of invoices. On election of an early payment, a charge is incurred by the supplier based on the period of acceleration, central bank interest rate, and the rate agreed between Taulia Inc. and each supplier. All early payments are paid by Greensill Capital, and AstraZeneca settles the original invoice amount with Greensill Capital at maturity of the original invoice due date.

We believe this programme offers a benefit to our suppliers, as it provides visibility and flexibility to manage their cash flow, and the rates offered can be preferential to their cost of funding. The programme is currently live in the US, UK, Sweden and Germany. As of December 2018, the programme had 2,548 suppliers enrolled, and a potential early payment balance of $166 million.

For more information on supply chain financing, see Note 19 on page 177.

For more information on Ethical supply chain management, see from page 45.

Manufacturing capabilities

Our principal tablet and capsule formulation sites are in the UK, Sweden, China, Puerto Rico and the US, with local/regional supply sites in Russia, Japan, Indonesia, Egypt, India, Germany, Mexico and Brazil. We also have major formulation sites for the global supply of parenteral and/or inhalation products in the US, Sweden, France, Australia and the UK. Most of the manufacture of APIs is delivered through the efficient use of external sourcing that is complemented by internal capability in Sweden.

For biologics, our principal commercial manufacturing facilities are in the US (Frederick, MD; Greater Philadelphia, PA), the UK (Speke), and the Netherlands (Nijmegen), with capabilities in process development, manufacturing and distribution of biologics, including global supply of mAbs and influenza vaccines. In Sweden, our new biologics drug product manufacturing facility became available at the end of 2018.

As part of our ongoing review of manufacturing capabilities and capacity, in January 2019, we made the decision to discontinue operations at the Boulder and Longmont, CO manufacturing facilities to increase efficiencies in our global biologics supply chain. This step will consolidate our biologic drug substance manufacturing network to one large-scale drug substance facility, the Frederick Manufacturing Center, MD. The closure of the sites is expected to be completed by the end of 2019 and will not impact the supply or global availability of any of our biologic medicines. We will be working with the impacted employees to provide outplacement and transition support.

For small molecules we have constructed a new small-scale development and launch facility alongside our existing manufacturing facility in Wuxi, China. This investment supports the acceleration of delivery of new innovative medicines to patients in China and completes our ability to execute across the whole life-cycle of medicines from discovery to commercialisation.

At the end of 2018, approximately 13,000 people were employed at 29 Operations sites in 17 countries.

29

We have 29 Operations sites in 17 countries

260

Completed more than 260 major or strategically important business transactions in the last three years, including 80 in 2018

630

We have more than 630 collaborations worldwide

"As part of our planning to manage the impact of the UK leaving the EU, we have engaged with regulators and government to ensure they have a clear view on the potential impact on pharmaceutical supply chains."

Partnering

Business development, specifically partnering, is an important element of our business. It supplements and strengthens our pipeline and our efforts to achieve scientific leadership. We partner with others around the world, including academia, governments, industry, scientific organisations and patient groups, as well as other pharmaceutical companies, to access the best science to stimulate innovation and accelerate the delivery of new medicines to target unmet medical need. We currently have more than 630 collaborations around the world.

More generally, our business development activity takes many forms and can be broadly grouped into:

> alliances, collaborations and acquisitions to enhance our portfolio and pipeline in our main therapy areas
> externalisation activity to maximise the value of our assets
> divestments of non-priority medicines.

We continue to assess opportunities to make strategic, value-enhancing additions to our portfolio and pipeline in our main therapy areas, including through in-licensing and acquisitions. No acquisitions were completed in 2018.

Over the past three years, we have completed more than 260 major or strategically important business development transactions, including some 80 in 2018. Of these transactions, eight were related to pre-clinical assets or programmes and 38 to precision medicine and biomarkers associated with small molecule and biologics programmes. Thirteen transactions helped expand our biologics capabilities.

Of particular note, we announced a new agreement with Innate Pharma under which we will exercise our existing option to obtain full oncology rights to monalizumab, a first-in-class humanised anti-NKG2A antibody which has demonstrated positive Phase II results in head and neck cancer and presents opportunities in colorectal cancer and haematological malignancies as well (see Oncology therapy area review, from page 50 for further details). The agreement also provides us with access to Innate Pharma's anti-CD39 mAb, IPH5201, plus four additional immuno-oncology molecules, increasing the breadth and depth of our immuno-oncology portfolio. As part of this transaction, we also licensed US commercial rights for *Lumoxiti* to Innate Pharma.

In addition, we entered into an agreement under which AstraZeneca will gain the exclusive rights from Zambon to import, distribute and promote *Fluimucil* ampoules, a medicine which treats respiratory disease, for inhalation in China (excluding Hong Kong, Macau and Taiwan).

Externalisation is a core component of our strategy and has an important role to play in the delivery of our ambition as we continue to sharpen our focus on developing key assets within our main therapy areas. This activity creates additional value from our existing medicines as well as recurring Externalisation Revenue and falls broadly into two categories:

> collaborations that help us access therapy area expertise
> collaborations that help us increase the number of patients and the reach of medicines in which we maintain an ongoing interest, but which typically sit outside our main therapy areas.

Details of significant business development transactions which give rise to Externalisation Revenue are included in the Financial Review from page 74. The Externalisation Revenue generated in 2018 is provided in Note 1 from page 160. There were no significant transactions during 2018.

We also divest medicines that typically sit outside our main therapy areas and that can be deployed better by a partner, in order to redirect investment and resource in our main areas of focus, while ensuring continued or expanded patient access. For example, in 2018, we divested European rights for *Atacand* to Cheplapharm; European rights for *Nexium* to Grünenthal; rights for *Seroquel* in all except the US and European markets to Luye Pharma; rights for *Vimovo*, excluding the US and Japan, to Grünenthal; and rights to *Alvesco*, *Omnaris* and *Zetonna* in all markets except the US to Covis. We also entered into an agreement with Sobi to divest the US rights for *Synagis*, the agreement was signed in November 2018 and the transaction completed in January 2019. In addition, we spun out six molecules from our early-stage inflammation and autoimmunity programmes into an independent biotech company, Viela Bio (see Other Disease Areas therapy area review, from page 67 for further details). These agreements will enable us to concentrate our resources on bringing multiple new medicines to patients.

The resulting revenue from these activities supports our R&D investments in our main therapy areas. A total of 15 transactions that contribute to Externalisation Revenue or generate income through divestment or out-licensing were completed in 2018.

More information on our partnering activity in 2018 can be found in the Financial Review from page 74 and Notes 1 and 2 to the Financial Statements from page 160.

Intellectual Property

Our industry's principal economic safeguard is a well-functioning system of patent and related protection that recognises our efforts and rewards innovation with appropriate protection – and allows time to generate the revenue we need to reinvest in pharmaceutical innovation. Patent rights are limited by territory and duration.

A significant portion of a patent's term can be spent during R&D, before it is possible to launch the protected product. Therefore, we commit significant resources to establishing and defending our patent and related IP protections for inventions.

Patent process

We file patent protection applications for our inventions to safeguard the large investment required to obtain marketing approvals for potential new drugs. As we further develop a product and its uses, these new developments may necessitate new patent filings. We apply for patents through government patent offices around the world. These assess whether our inventions meet the strict legal requirements for a patent to be granted. Our competitors can challenge our patents in patent offices and/or courts. We may face challenges early in the patent application process and throughout a patent's life. The grounds for these challenges could be the validity of a patent and/or its effective scope and are based on ever-evolving legal precedents. We are experiencing increased challenges in the US and elsewhere in the world (such as in Australia, Brazil, Canada, China, Europe and Japan), and there can be no guarantee of success for either party in patent proceedings.

For information about third-party challenges to patents protecting our products, see Note 29 to the Financial Statements from page 194.

For more information on the risks relating to patent litigation and early loss and expiry of patents, see Risk from page 220.

The basic term of a patent is typically 20 years from the filing of the patent application with the relevant patent office. However, a product protected by a pharmaceutical patent may not be marketed for several years after filing, due to the duration of clinical trials and regulatory approval processes. Patent Term Extensions (PTEs) are available in certain major markets, including the EU and the US, to compensate for these delays. The term of the PTE can vary from zero to five years, depending on the time taken to obtain any marketing approval. The maximum patent term, when including PTE, cannot exceed 15 years (EU) or 14 years (US) from the first marketing authorisation.

Patent expiries

The table on pages 217 to 219 sets out certain patent expiry dates and sales for our key marketed products.

Other exclusivities

Regulatory data protection (RDP or 'data exclusivity') is an important additional form of exclusivity which is separate from, but runs in parallel to, patent exclusivity. RDP arises in respect of data which is required to be submitted to regulatory authorities to obtain marketing approvals for our medicines. Significant investment is required to generate such data (for example, through conducting global clinical trials) and this proprietary data is protected from use by third parties (such as generic manufacturers) for a number of years in a limited number of countries. The period of such protection, and the extent to which it is respected, differs significantly among countries and varies depending on whether an approved drug is a small or large molecule compound. RDP is an important protection for our products, and we strive to enforce our rights to it, particularly as patent rights are increasingly being challenged.

The RDP period starts from the date of the first marketing approval from the relevant regulatory authority and runs parallel to any patent protection. For small molecule drugs, RDP generally expires prior to patent expiry in all major markets.

If a product takes an unusually long time to secure marketing approval, or if patent protection has not been secured, has expired or has been lost, then RDP may be the sole right protecting a product from copying. Generic manufacturers, we believe, should not be allowed to rely on AstraZeneca's data to support the generic product's approval or marketing until the RDP right has expired. In the EU, the RDP period is eight years followed by two years' market exclusivity.

In the US, new chemical entities (NCEs) are entitled to a period of five years of RDP under the Federal Food, Drug and Cosmetic Act. This period of RDP runs parallel to any pending or granted patent protection and starts at the approval of the new application. There are circumstances where RDP could be the sole layer of exclusivity protecting a product from being copied. Further, under the Biologics License Application process, the FDA will grant 12 years' data RDP for a new biologic to an innovator manufacturer.

Under Orphan Drug laws in the EU and US, market exclusivity is granted to an innovator who gains approval for a pharmaceutical product developed to treat a rare disease. What qualifies as a rare disease differs between the EU and US. Qualifying Orphan Drugs are granted 10 years' market exclusivity in the EU and seven years' market exclusivity in the US.

Compulsory licensing

Compulsory licensing (where a Patent Authority imposes a licence on the Patentee) is on the increase in certain markets in which we operate. We recognise the right of developing countries to use the flexibilities in the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (including the Doha amendment) in certain circumstances, such as a public health emergency. We believe this should apply only when all other ways of meeting the emergency needs have been considered and where healthcare frameworks and safeguards exist to ensure the medicines reach those who need them.

Information technology and information services resources

In 2018, we continued to sharpen our focus on running IT with high quality performance – improving IT cost efficiency, systems performance and delivering higher levels of support for business priorities.

With the IT foundation now firmly in place and operating at high levels of efficiency, we have started to shift our focus to drive more transformative and digital capabilities to support the evolving needs of the business. We have a growing programme portfolio which will see us take advantage of data and analytics, artificial intelligence, digital and the Internet of Things – all of which are key to support our overall business transformation. In order to deliver on these commitments, IT has actively been strengthening its capabilities through recruiting key external talent into the organisation, as the expertise to succeed in some of these technologies was not internally present at the levels needed. In addition to recruiting leaders in new technologies, the IT organisation continues to harness internal capabilities, enabling us to accelerate drug development, revenue growth and profitability.

Cybersecurity

The cybersecurity threat landscape continues to grow in both volume and complexity, with the healthcare industry increasingly becoming a target of cyber criminals. Protecting our IT systems, IP and confidential information against cyber crimes continues to be a critical area of focus and investment. Our implementation of the National Institute of Standards & Technology (NIST) risk framework allows us to understand cyber resilience and risk positioning, improving our ability to prevent attacks and minimise damage and data loss should a breach occur. We have seen success with our mandatory employee cybersecurity awareness training programme, which helps employees recognise and defend against common and high-risk cyber threats.

Our 'Defense in depth' strategy has focused on enhancing multiple levels of protection and detection as well as introducing additional third-party cybersecurity intelligence with an appropriate response from our 24x7 Security Operations Centre. Cybersecurity testing via both internal and external cybersecurity teams will continue to validate our cyber maturity and risk. We continue to develop our relationships with government agencies, third-party cybersecurity professionals, and many cybersecurity-related peer groups. Cybersecurity within our third-party vendors and supply chains is a focus area for AstraZeneca. As an ongoing process, we are evaluating reasonable levels of security and associated controls, requiring contractors, vendors and critical supply chain partners to meet or exceed our cybersecurity standards.

For more details, including the risks relating to information technology and cyber threats, see Risk from page 220.

Science *can* deliver complete disease management in China

Opened in 2017, and jointly developed with partners from government, industry and academia, as well as with research and medical institutions, our China Commercial Innovation Centre in Wuxi in Jiangsu Province is designed as a showcase for innovative ideas in healthcare. It uses the Internet of Things (IoT), big data, artificial intelligence and other digital technologies to meet the needs of patients in disease prevention, screening, diagnosis, treatment and rehabilitation.

We collaborate with companies who use advanced technologies to make diagnosis more precise, effectively combine drugs with medical devices for better treatment, and integrate online and offline healthcare resources to make information more accessible. In this way, we can develop complete disease management solutions that deliver better outcomes for patients, make healthcare more accessible, and improve the understanding and management of diseases.

We currently have eight models for disease management which continue to be rolled out, not only across Wuxi, but across the whole of China:

- Chronic disease management – 42 centres
- China chest pain – 783 centres
- Metabolic management – 200 centres
- Gastrointestinal cancer – 66 centres
- Integrated centre for lung cancer treatment – 20 centres
- Integrated centre for prostate cancer diagnosis and treatment – 200 centres
- Paediatric nebulisation – 15,000 centres, including 4,200 smart centres
- Pulmonary and critical care medicine – 593 centres

593
Pulmonary and critical care medicine centres

3. Be a Great Place to Work

Great people are central to our success and being a great place to work is at the heart of our efforts to foster the talents of our people. We promote a culture, both for employees and those third parties with whom we work, that delivers sustainable good performance and long-term business success.

Overview

- Encouraging improvements in scores in our employee survey (Pulse)
- Continued development of women and increase in the representation of women in senior roles
- Published new Global Standards on inclusion and diversity, sexual harassment and bullying, reinforced by training
- Continued focus on workforce planning to attract critical capabilities and manage retention risks
- Maintained listing in Pharmaceuticals, Biotechnology and Life Sciences industry group of Dow Jones Sustainability Index
- Materiality assessment reaffirmed focus and used to refine our sustainability priorities
- Sustainability Advisory Board met twice in 2018 to guide, recommend opportunities and provide external feedback
- Continued progress towards our target to source 100% renewable power by 2025

Employees

To achieve our strategic priorities, we continue to attract, retain and develop a talented and diverse workforce united in the pursuit of our Purpose and living our Values.

We value the talents and skills of our employees and our people strategy supports our strategic priority of being a Great Place to Work.

Build and develop organisations and capabilities

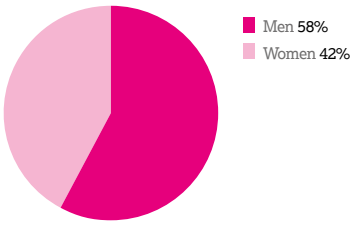
We are developing strategic workforce plans to ensure we can attract the critical capabilities required to deliver our long-term strategic priorities. These plans are underpinned by predictive analytics, meaning workforce decisions are data-driven. We also use workforce analytics to ensure that we manage our global workforce optimally. In addition, we have implemented a significant number of automation initiatives to allow our workforce to spend a higher proportion of their time on higher-value activity.

We have implemented a talent scout model to enhance our ability to attract key talent into senior roles. This has been successful, demonstrating our ability to hire best-in-class critical capability at a reduced cost. This has been supported by an enhanced employee referral scheme, which has become an increasingly important source of hire. This scheme won a significant external award.

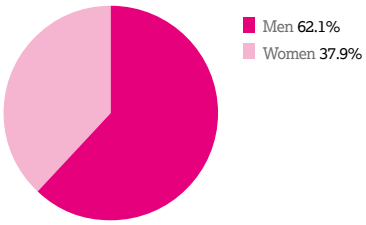
We are working to attract emerging talent, as well as investing in internships and recruitment opportunities globally. For example, we conduct a global programme to hire recent graduates for pharmaceutical technology and development, procurement, quality, engineering, IT, supply chain, and biometrics and information sciences functions. We also ran a graduate programme for IMED, which complements our established IMED Post Doctorate Programme for researcher recruitment. Additionally, we offer a 12-week internship opportunity for business school students to contribute to key initiatives in our Oncology therapy area.

Gender diversity

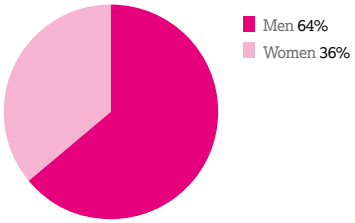
Board of Directors of the Company



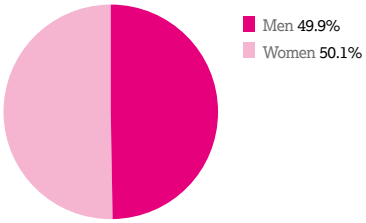
Directors of the Company's subsidiaries*



Senior Executive Team*



AstraZeneca employees



* For the purposes of section 414C(8)(c)(ii) of the Companies Act 2006, 'Senior Managers' are the Senior Executive Team (SET), the directors of all of the subsidiaries of the Company and other individuals holding named positions within those subsidiaries.

All numbers as at 31 December 2018.

During 2018, we hired 13,000 permanent employees. Hiring over recent years means that employees with less than two years' service now represent 33% of our global workforce (up from 20% in 2012). This provides a greater balance in terms of refreshing talent and retaining organisational experience. The majority of this hiring has been focused in our Emerging Markets, in particular China, as we continue to reshape our workforce footprint to support our strategic objectives and to position us well for the future. Our data indicates that these recent hires are performing strongly, although in some areas of the business retention of this population is challenging.

Voluntary employee turnover increased slightly to 10.2% (2017: 9.7%). The voluntary employee turnover rate among our high performers decreased in 2018 to 6.6% (2017: 7.1%), while the voluntary employee turnover of recent hires increased to 14.5% (2017: 12.2%). We seek to reduce regretted turnover through more effective hiring and induction, exit interviews, risk assessments and retention plans.

The uncertainty faced by individuals and their families following the UK's decision to leave the EU could have an impact on hiring and retaining staff in some business-critical areas. Consequently, we are providing extensive support and information to employees who might be impacted, monitoring trends in recruitment and resignation closely, and also guiding new hires through our recruitment process.

Drive a vibrant, high-performing culture

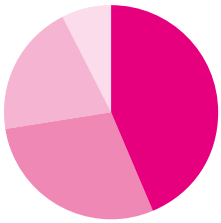
Continuing our emphasis on high performance, in 2018, our high performers were promoted at twice the rate of the wider employee population. We require every employee to have high-quality objectives, aligned to our strategy, which we monitor closely. Managers are accountable for working with their employees to develop individual and team performance targets, and for ensuring employees understand how they contribute to our overall business objectives. Through increased investment in technology, we have also extended our global annual salary and incentive review process to cover 90% of employees (2017: 87%). We encourage participation in various employee share plans, some of which are described in the Directors' Remuneration Report from page 120, and also in Note 28 to the Financial Statements from page 192. Additionally, in the UK, we are making changes to the way we reward, provide benefits and support our people. These changes are designed to rebalance the reward mix, improve understanding of benefits and simplify our processes.

Our salary and bonus budgets are distributed in line with our principles, allowing us to clearly differentiate reward according to performance.

We are committed to hiring and promoting talent ethically and in compliance with applicable laws. Our Code of Ethics and its supporting Standards are designed to help protect against discrimination on any grounds (including disability) and cover recruitment and selection, performance management, career development and promotion, transfer, training, retraining (including retraining, if needed, for people who have become disabled), and reward. Our Global Standard for Inclusion and Diversity sets out how we

A global business

Employees by reporting region



64,600
employees

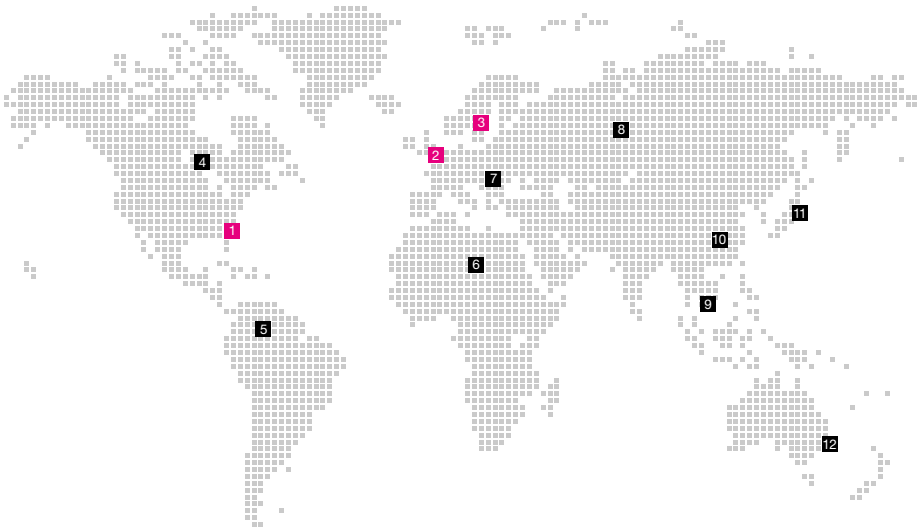
Co-locating around three strategic R&D centres

1. Gaithersburg, MD, US
3,200

2. Cambridge, UK
2,500

3. Gothenburg, Sweden
2,200

By geographical area



1. US
12,800
19.8%

2. UK
7,400
11.4%

3. Sweden
6,300
9.8%

4. Canada
800
1.3%

5. Central and South America
3,100
4.9%

6. Middle East and Africa
1,700
2.6%

7. Other Europe
7,400
11.5%

8. Russia
1,000
1.6%

9. Other Asia Pacific
6,900
10.6%

10. China
13,200
20.5%

11. Japan
3,000
4.6%

12. Australia and New Zealand
1,000
1.6%

All numbers as at 31 December 2018.

foster an inclusive and diverse workforce where everyone feels valued and respected because of their individual ability and perspective. It describes the principles of our commitment and provides a framework for developing and implementing the people plans needed to ensure we deliver these principles consistently worldwide. More information on our Global Policy framework can be found on page 43, our Code of Ethics on page 105, and our Global Policies and Standards can be found on our website, www.astrazeneca.com/sustainability.

Employee opinion surveys help us measure employee satisfaction and engagement, and progress in our aim of being a great place to work. Comparing our most recent survey (December 2018) to the previous year (December 2017), of the 17 items common to both surveys, we improved in 11 items, remained stable for four and saw minor reductions (-1%) in the score for two items. Importantly, we scored highly for 'understanding of the future direction and strategy', and we saw good progress in 'opportunities for personal development and growth' and items around inclusion and diversity (where we are above the global high-performing norm). We also exceeded our scorecard target for 'I would recommend AstraZeneca as a great place to work'. Despite progress in the latest survey, there remains further opportunity for improvement around leadership communication and prioritisation.

Develop a strong and diverse pipeline of leaders

To foster innovation, we seek to harness different perspectives, talents and ideas as well as ensuring that our employees reflect the diversity of the communities in which we operate.

As part of our commitment to inclusion and diversity, we have implemented numerous initiatives across the globe, such as unconscious bias training, the formation of various employee resource groups (such as an LGBT+ network) and updated recruitment standards to ensure diverse candidate lists.

Our commitments include a goal to increase the number of women on our leadership teams. As shown in the gender diversity figure on page 38, women comprise 50.1% of our global workforce. There were five women on our Board (42% of the total) at the end of 2018 (Shriti Vadera retired with effect from 1 January 2019). Below Board level, the representation of women in senior roles (ie roles at Career Level F or above which constitute the six highest bands of our employee population) increased to 44.6% in 2018 (2017: 44.4%), which exceeded our scorecard target of 44.4% for this measure and compares favourably to external benchmarks. Women are also currently promoted at a higher rate than men across all levels of seniority, positively impacting the gender balance. In 2018, AstraZeneca was ranked 12th in the FTSE 100 for Women on Boards and seventh for Women on Executive Committees and Direct Reports.

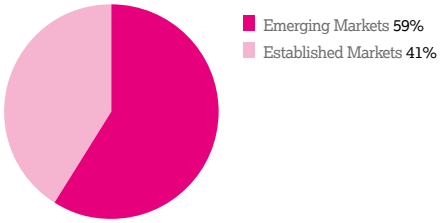
Our Women as Leaders programme aims to encourage more women into senior roles – approximately 600 women had completed the programme by the end of 2018. Of those who provided feedback, 55% have either been promoted, or had their remit expanded, or been identified for future promotions. In addition, we have developed women's networks in most countries, continued to hold women's summits in various locations around the world and continued to support mentoring relationships, for example introducing mentoring by senior women for emerging talent in Operations.

In 2018, 80% of vacancies across the top three levels of our organisation were filled internally, reflecting our long-term commitment to develop high-quality leaders and the rigour of our leadership succession planning. To ensure our senior leadership reflects our diverse geographic footprint, we track the country of origin of senior leaders and reflect this in our diversity targets. In 2018, 19.4% of employees who are either members of the SET, or their direct reports, have a country of origin that is an Emerging Market or Japan (an increase from 5% in 2012 and ahead of our 2018 target of 15%).

Diversity is integrated into our Code of Ethics and associated workforce policy. In addition to the two diversity metrics tracked in the AstraZeneca scorecard (representation of women in senior roles and senior leadership country of origin that is an Emerging Market or Japan), on a bi-annual basis, the SET and Board are provided with a comprehensive overview of the AstraZeneca workforce, covering a wide range of metrics and measures (including trends around gender diversity, leadership ethnic diversity and age profile). The SET is also provided with a quarterly summary of key workforce metrics, including gender diversity and leadership ethnic diversity. Within the US, we track overall ethnic minority representation, ethnic minority representation in senior roles, and ethnic minority representation in succession plans.

In addition to the Global Standard on Inclusion and Diversity, in 2018 we published new Global Standards on sexual harassment and bullying. Drawing on our commitment to respect and equal opportunity, we aim to build a culture where everyone feels safe to 'speak up'. This is important, not just for those who feel they have seen or experienced unwelcome attention or behaviour, but also to ensure that colleagues recognise the value they bring when they share their different perspectives and ideas. This is integral to making the most of our diversity of thought, because it is the foundation of our ability to innovate. The Standards are being reinforced by specific training and education across the organisation on the importance of speaking up (which includes challenging behaviours that are inconsistent with our Values and Code of Ethics), demonstrating inclusive leadership and responding to allegations of misconduct. We have multiple channels available for reporting. Allegations are taken very seriously and handled in a manner that is sensitive to the confidentiality and security of those making a report and will be subject to global oversight.

Sales and Marketing workforce composition



Generate a passion for people development

We encourage employees to take ownership of their own development and expect leaders to spend time supporting their employees' development. To support this, we have implemented a global platform to increase the visibility and accessibility of job opportunities and received over 22,000 applications from internal candidates through this platform in 2018.

In 2017, we implemented a best-practice cloud-based global learning management system to ensure that opportunities to learn are available to all employees. In 2018, we continued to leverage this technology as part of our ambition to continuously transform the learning culture in AstraZeneca.

Following the successful launch of 'Leading People' in 2017 (a social online learning platform aimed at managers), 'Leading Self' was rolled out across the organisation aimed at employees below manager level. Over 5,400 employees have accessed this innovative, social online learning experience. In 2018, we piloted our 'Leading Business' programme, connecting 100 managers from all areas and regions of AstraZeneca to develop their leadership capability. We continue to see a positive impact of these experiences in engagement and retention measures.

Human rights

Our Code of Ethics and Human Rights Statement commit us to respecting and promoting international human rights – not only in our own operations, but also in our wider spheres of influence, such as our third-party providers. To that end, we integrate human rights considerations into our processes and practices. We are also committed to ensuring that there is no modern slavery or human trafficking in our supply chains or any part of our business. Our full statement required under section 54 of the UK Modern Slavery Act is available on our website, www.astrazeneca.com.

We support the principles set out in the United Nations Universal Declaration of Human Rights and the International Labour Organization's (ILO) standards on child labour and minimum wages. We have been members of the United Nations Global Compact on Human Rights since 2010.

We measure human rights by means of a labour review survey every two years in all countries where we have a presence. The review focuses on ILO core themes, including freedom of association and collective bargaining, child labour, discrimination, working hours and wages, including questions on the Living Wage. Where local gaps to ILO minimum standards are identified, such as maternity leave or grievance procedures, we put in place local plans to close those gaps where allowed by relevant national legislation. Our reporting in this area is assured by Bureau Veritas.

For more information about the assurance provided by Bureau Veritas, see page 231.

In 2017, we signed up to the 'Fair Wage' database. These data are being used in our end of 2018 survey to measure performance more independently and to inform future direction in the fair/living wage space.

Managing change

We continue to implement plans to invest in our three strategic R&D centres in the US, UK and Sweden. We encourage and support employees to relocate and have made good progress. For example, of the more than 2,500 employees working in Cambridge, 569 have relocated from other sites in the UK. In addition to the 1,100 employees hired between 2015 and 2017, we hired a further 452 permanent employees in Cambridge in 2018. We are using interim infrastructure in and around Cambridge to house these employees until our new site on the Cambridge Biomedical Campus is ready. For employees who do not accept offers to relocate to Cambridge, we provide career support, outplacement support and competitive severance packages.

For more information on this move, see Cambridge on page 27.

As outlined in the Manufacturing capabilities section on page 34, in January 2019 we made the difficult decision to discontinue operations at our biologics manufacturing facilities at Boulder and Longmont CO, US.

In January 2019, we announced plans to realign R&D and parts of our Commercial business to ensure we can execute on our priorities and strategy. We have established dedicated teams who, guided by a clear set of People Principles, will ensure the transition is executed as quickly as possible, keep our employees regularly informed and treat them fairly, and comply with local legislative and HR policies and practices, including consulting with employee representatives as required.

For more information on our restructuring programme, see the Financial Review from page 74.

Employee relations

We seek to follow a global approach to employee relations guided by global employment principles and standards, local laws and good practice. We work to develop and maintain good relations with local workforces and work closely with our recognised national trade unions. We also regularly consult with employee representatives or, where applicable, trade unions, who share our aim of retaining key skills and mitigating job losses. According to our internal Human Rights survey carried out in 2016, 58% (106 countries surveyed) of countries in which AstraZeneca operates recognise and have a relationship with trade unions. Where trade unions do not exist in an area of operation, 99% of countries have established arrangements to engage similarly with their workforce. Our most recent survey commenced in October 2018, with conclusions due at the end of February 2019.

Safety, health and wellbeing

We work to promote a safe, healthy and energising work environment for employees and partners. Our standards apply globally and are stated in our Code of Ethics available on www.astrazeneca.com/sustainability. Due diligence includes establishing and monitoring a set of safety, health and wellbeing targets aimed at supporting our people and keeping AstraZeneca among the sector leaders in performance. Our reporting in this area is in the Sustainability Data Summary available on www.astrazeneca.com/sustainability and is assured by Bureau Veritas.

For more information about the assurance provided by Bureau Veritas, see page 231.

Safety

Vehicle collisions

Year	Collisions per million km	Target
2018	**3.74**	**3.58**
2017†	4.05	3.76
2016†	4.66	4.00
2015 baseline	4.13	

Work-related injuries

Year	Reportable injury rate per million hours worked	Target
2018	**1.31**	**1.50**
2017†	1.48	1.60
2016†	1.57	1.69
2015 baseline†	1.78	

† Data re-stated.

As shown above, we made further progress against our strategic targets in 2018, achieving a 26% reduction in the work-related injury rate and a 9% reduction in vehicle collision rate from the 2015 baseline. In addition, there were no work-related fatalities during 2018. Building on our previous success in establishing a culture of health and wellbeing, we continue to focus on active health promotion. We have programmes to address all four essential health activities – healthy eating and drinking, physical activity, tobacco cessation and mental wellbeing – at 65% of our sites.

In 2018, we carried out several activities and initiatives focused on continuous improvements in key risk areas, including driver safety (our highest risk for significant injury and fatalities), behavioural safety, ergonomics, office safety, fall prevention, workplace pressure management and work-life balance.

Sustainability

We want to be valued and trusted by our stakeholders as a source of great medicines over the long term. That is why we are committed to operating in a way that recognises the interconnection between business growth, the needs of society and the limitations of our planet. This means delivering our business strategy in a way that broadens access to our medicines, minimises the environmental footprint of our products and processes, and ensures that ethics and transparency underpin everything we do.

Sustainability strategy

Our sustainability strategy is aligned with our Purpose and business strategy, allowing us to maximise the benefit for our patients, our business, broader society and the planet. In late 2018, a structured sustainability materiality assessment that engaged external and internal stakeholders reaffirmed our direction and refined the priority areas. We measure our progress through annual and long-term targets. We show performance in our Sustainability Data Summary located on www.astrazeneca.com/sustainability.

Learn more in our 2018 Sustainability Report available on our website, www.astrazeneca.com/sustainability.

1. Broadening access to healthcare

We aim to improve lives by increasing access to health

Priority areas	Information in this Annual Report
> Disease prevention and treatment > Affordability > Investments in health systems > Responsible R&D > The environment's impact on health	> Emerging market healthcare, from page 32 > Broadening access to healthcare, on page 43

2. Furthering ethics and transparency

We commit to furthering ethics and transparency in everything we do

Priority areas	Information in this Annual Report
> Ethical business culture > Inclusion & diversity > Talent & workforce evolution > Workforce wellbeing and safety > Responsible supply chain > Human rights	> Code of Ethics and policy framework, on page 43 > Bioethics and responsible research, from page 44 > Develop a strong and diverse pipeline of leaders, on page 40 > Managing change and Employee relations, on page 41 > Safety, health and wellbeing, on page 41 > Ethical supply chain management, from page 45 > Human rights, on page 41 > Community investment, on page 48

3. Protecting the environment

We strive to reduce environmental impacts on human health and the natural world

Priority areas	Information in this Annual Report
> Greenhouse gas emissions > Waste > Water > Product environmental stewardship > Pharmaceuticals in the environment	> Greenhouse gas, on page 46 > Waste, on page 47 > Water, on page 47 > Product environmental stewardship, on page 47 > Pharmaceuticals in the environment, on page 47

Benchmarking and assurance

Recognition of our work in sustainability

DJSI	> Named in the Dow Jones Sustainability World and Europe Indices > Attained industry-best scores for: Environmental Reporting, Labour Practice Indicators and Health Outcome Contribution
ATMI	> Ranked ninth overall in the 2018 Access to Medicine Index > Recognised for a Best Practice in Pricing and one of nine companies recognised for an Innovative Practice
CDP	> Water A List – among the top 1.5% of companies participating in CDP's water security programme for our commitment to transparency around environmental risks and demonstration of sustainable water management > Climate change B List – in recognition of our strategy and actions to reduce emissions and mitigate climate change > Supplier Engagement leader board – among the top 3% of companies assessed by CDP to be awarded a position on the leader board in recognition of our actions to reduce emissions and lower climate-related risks in the supply chain
ISAE3000 Assured	> Bureau Veritas has provided independent external assurance to a limited level in accordance with the International Standard on Assurance Engagements 3000 (ISAE3000), and in accordance with ISAE3410 Assurance Engagements on Greenhouse Gas Statements for the sustainability information contained within this Annual Report and Form 20-F For more information, see Sustainability: supplementary information on page 231 and the letter of assurance available on www.astrazeneca.com/sustainability.

Sustainability governance

Sustainability governance frames the way we operate. Geneviève Berger, a Non-Executive Director, oversees the implementation of our sustainability matters on behalf of the Board of Directors. Our ambition is to be a leader in sustainability by delivering the strategy from the materiality assessment. Every member of the SET is accountable for a specific sustainability initiative and Katarina Ageborg is responsible for the global strategy.

Our Sustainability Advisory Board (SAB) comprises five SET members and four external sustainability experts. It met twice in 2018 to provide guidance on strategic direction, recommendations for opportunities, and insights and feedback. Throughout the year, we engaged with employees and external stakeholders, including investors, Ministries of Health, healthcare providers, NGOs, patients and suppliers.

1. Broadening access to healthcare

Marketplace from page 11 demonstrates the burden of NCDs, with 41 million deaths annually which disproportionately affects low- and middle-income countries where nearly three quarters of these deaths occur. In Return to Growth from page 29, we review how, as a business focused on medicines for NCDs, we aim to meet the challenges posed in each of our Regions, particularly for those patients in Emerging Markets who may need help to access our medicines and where barriers to healthcare are not always pricing related.

Our activities demonstrate how we are working to improve access to healthcare by making our medicines available and more affordable to people on a commercially and socially sustainable basis. Through partnerships with government and NGOs, we develop health systems' infrastructure by building capacity to help improve access to medical treatment and care.

Disease prevention is the focus of the Young Health Programme (YHP), our award-winning global disease prevention programme.

For more information on YHP, see page 48.

To address local needs, our programmes are typically governed by their respective commercial markets. The process includes setting and measuring performance towards targets. We have internal targets and our annual Sustainability Report lists our external targets and progress. We undergo third-party assurance for these external targets and our reporting in this Annual Report is assured by Bureau Veritas – for more information see page 231.

2. Ethics and transparency

We want to be valued not only for our medicines but also for the way we work. We seek to operate in a transparent and ethical way and expect the same high standards from our suppliers and partners. Whether it is investing in technological alternatives to animals in science for our research or refusing to tolerate bribery or any other form of corruption, we aim to go beyond what is required of us to be an example of how good business is done.

Code of Ethics and policy framework

We are committed to employing high ethical standards when carrying out all aspects of our business globally. Our Code of Ethics (the Code) is based on our Values, expected behaviours and key policy principles. It empowers employees to make decisions in the best interests of the Group and the people we serve, now and in the long term, by outlining our commitments in simple terms and focusing on why these commitments matter. The Code also guides employees on how to make the best day-to-day choices and how to act in a consistent, responsible way, worldwide. There are two mandatory training courses dedicated to the Code: one is for new starters; the second is the annual training for all employees, reminding them of the key commitments. In 2018, 100% of all active employees completed the annual training on the Code of Ethics.

The Code includes four high-level Global Policies covering Science, Interactions, Workplace and Sustainability. These Global Policies will continue to be complemented by underlying Global Standards and will, over time, replace the current suite of Global Policies which are published on our website, www.astrazeneca.com. Our policy framework also includes additional requirements at the global, local and business unit level to support employees in their daily work.

Ethical sales and marketing

We are committed to employing high ethical standards of sales and marketing practice worldwide, in line with our policy framework. We maintain a robust compliance programme in our efforts to ensure compliance with all applicable laws, regulations and adopted industry codes. As outlined in Global Compliance and Internal Audit Services on page 105, our compliance programme is delivered by dedicated compliance professionals who advise on and monitor adherence to our policy framework.

These professionals also support our line managers locally in ensuring that their staff meet our standards. A network of nominated signatories reviews our promotional materials and activities against applicable requirements. Our Internal Audit Services, in partnership with external audit experts, also conduct compliance audits on selected marketing companies. Our reporting in relation to ethical sales and marketing is assured by Bureau Veritas.

For more information about the assurance provided by Bureau Veritas, see page 231.

Approximately 36,100 employees are engaged in our commercial activities and, in 2018, we identified four confirmed breaches of external sales and marketing regulations or codes (2017: six). There were 2,042 instances, most of them minor, of non-compliance with the Code or supporting requirements in our Commercial Regions, including instances by employees and third parties (2017: 1,431). We removed a total of 169 employees and third parties from their roles as a result of these breaches (a single breach may involve more than one person). We also formally warned 534 others and provided further guidance or coaching on our policies to 1,865 more. The Audit Committee are provided with the breach statistics on a quarterly basis. Further commentary on the most serious breaches is also provided to the Audit Committee.

Anti-bribery/anti-corruption

Anti-bribery/anti-corruption is a key element of our policy framework, with principles and requirements underpinning the Code commitment that we do not tolerate bribery or any other form of corruption. We conveyed our commitment to ethical behaviour in the 2018 annual Code training, reinforced through anti-bribery/anti-corruption training materials delivered and made available to relevant employees and third parties.

Bribery and corruption remains a business risk as we launch new medicines in markets across the globe and enter into partnerships and collaborations. When working with third parties, we are committed to working only with those who embrace high standards of ethical behaviour consistent with our own. Bribery and corruption risk is a focus of our third-party risk management process, as well as our Business Development due diligence procedures. It is also a focus of our monitoring and audit programmes. Global Compliance monitors a range of commercial activities associated with bribery and corruption risk, and the majority of marketing company audits include anti-bribery/anti-corruption work programmes.

100%

100% of all active employees completed training on our Code of Ethics

"Our commitment to working in a transparent and ethical manner is essential to achieving scientific leadership and delivering life-changing medicines."

Transparency reporting

AstraZeneca is committed to the highest standards of conduct in all our operations, including the disclosure of payments to healthcare practitioners (HCPs), healthcare organisations (HCOs) and patient groups, with full transparency where recipients have provided consent and in accordance with all current obligations covering the 43 markets with reporting requirements. In the US, Europe, Australia and Japan our external transparency reporting meets the requirements of the Physician Payments Sunshine Act (Open Payments), European Federation of Pharmaceutical Industries and Associations (EFPIA) Disclosure Code, Medicines Australia (MA) Code of Practice, and the Japanese Pharmaceutical Manufacturers Association (JPMA) Disclosure Code, as well as applicable local and state transparency requirements. Further, we have progressive plans to expand our disclosure activities in another six markets across Canada, Latin America, Asia Pacific, North Africa and the Middle East regions over the next two years. We are progressively heading towards increased disclosure in additional markets globally and, in all locations, we are committed to ensuring payments are justified and reasonable.

Bioethics and responsible research

Our commitment to working in a transparent and ethical manner is essential to achieving scientific leadership and delivering life-changing medicines. 'Bioethics' refers to the range of ethical issues that arise from the study and practice of biological and medical science, and our Bioethics Policy sets out our principles in key subject matter areas. These principles apply to all our research activity, whether conducted by us or by third parties acting on our behalf. The following sections summarise our activities in the main areas, and our Bioethics Policy is available on our website, www.astrazeneca.com/sustainability.

Our Bioethics Advisory Group (BAG) is sponsored by the Chief Medical Officer and exists to oversee the operation of the Bioethics Policy. It acts as a source of bioethical advice to the business, bringing together the subject matter leads for each of the key bioethical areas, supported by other experts and specialists. BAG receives reports on governance and practice from subject matter leads, responds to requests for advice and support from the business, and carries out horizon-scanning activities to identify emerging scientific, technological and regulatory issues. BAG met six times in 2018. Ethical discussions in 2018 included the potential therapeutic use of human stem cells in patients, the implications of continuing advances in precise genome editing technologies, and issues around consent and withdrawal of consent for use of patient samples and data.

Clinical trials

We believe that transparency enhances the understanding of how our medicines work and benefit patients. At www.AstraZenecaClinicalTrials.com, we publish information about our clinical research, as well as the registration and results of our clinical trials – regardless of whether they are favourable – for all products and all phases, including marketed medicines, drugs in development and drugs where development has been discontinued.

In 2018, we conducted a range of clinical trials across regions as shown in the charts on the right. This broad span helps ensure that study participants reflect the diversity of patients for whom our medicines are intended and identifies the patients for whom the medicine may be most beneficial. Our global governance process provides the framework for ensuring a consistent, high-quality approach worldwide. Protecting participants throughout the trial process is a priority and we have strict procedures to help ensure participants are not exposed to unnecessary risks.

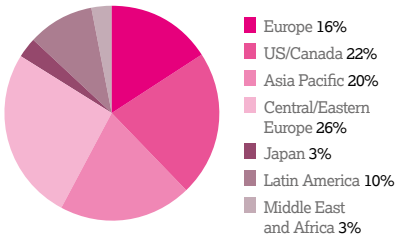
All our clinical studies are designed and finally interpreted in-house. Some are conducted by contract research organisations (CROs) on our behalf and we require these organisations to comply with our global standards.

As of 31 December 2018, we shared anonymised individual patient-level data from 136 studies with 37 research teams and responded to 111 requests from external researchers using our portal, http://astrazenecagroup-dt.pharmacm.com to request our clinical data and reports to support additional research. In 2018, we continued to participate in the industry-wide portal www.trialsummaries.com where we publish Trial Result Summaries in easy-to-understand language and translate these to the local language for all sites where a study is conducted. As of 31 December 2018, we published Trial Result Summaries for 66 AstraZeneca studies.

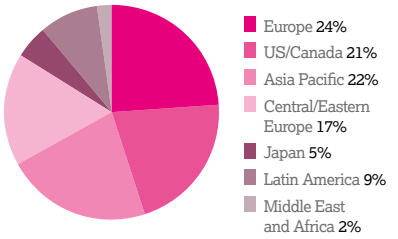
For more information, see our website, www.astrazeneca.com, or our clinical trials website, www.AstraZenecaClinicalTrials.com.

Clinical trials by region

Small molecule studies



Biologics studies



Patient safety

One of our core Values is to put patients first and, by detecting, assessing, understanding and preventing adverse effects or any other drug-related problems not identified during the development process, our pharmacovigilance processes and systems seek to minimise the risks and maximise the benefits of our medicines for patients.

For all our medicines, under development as well as on the market, we have systems in place for identifying and evaluating possible adverse drug effects. Information concerning the safety profile of our medicines is provided to regulators, healthcare professionals and, where appropriate, patients. Each medicine has a dedicated safety team, which includes a responsible global safety physician and one or more pharmacovigilance scientists. Marketing companies have assigned patient safety managers in place.

Our Chief Medical Officer is accountable for the benefit and risk profiles of our products, providing medical oversight and enforcing risk assessment processes that help us make efficient and informed decisions about patient safety. As part of our commitment to patient safety, in 2017, we developed an upgraded safety signal management platform to provide risk oversight for all our products. Following an extensive pilot test phase during 2018, we launched the platform across all marketed products and continue to seek refinements to make it an industry leader in pharmacovigilance. We also began exploring the use of emerging technologies, such as automation support, machine learning and digital communication interfaces. These tools will have the potential to enhance our product safety evaluation, communication and risk mitigation capabilities.

Research use of human biological samples

The use of human biological samples, such as solid tissue, biofluids and their derivatives, plays a vital role in developing a deeper understanding of human diseases and their underlying mechanisms, which helps us develop effective, new and personalised medicines.

When we conduct this important research, we maintain policies and processes to ensure that we comply with the law, meet regulatory concerns and maintain ethical standards. We place an emphasis on informed consent that protects the rights and expectations of donors and families throughout the process of our acquisition, use, storage and disposal of the samples. Protecting the confidentiality of a donor's identity is of the utmost importance, and a key part of our process includes the coding of biological samples and associated data (including genetic data).

In rare circumstances, we may use human fetal tissue (hFT) or human embryonic stem cells (hESC). In these circumstances, an internal review of the scientific validity of the research proposal will be conducted and permission to use the tissue will be granted only when no other scientifically reasonable alternative is available. We also insist our third-party vendors adopt the highest ethical standards and we rigorously assess the ability of tissue suppliers to meet our quality and ethical expectations. We are committed to minimising the use of fetal tissue by exploring technological alternatives.

In 2018, an additional research proposal that includes use of cells derived from hFT was approved, resulting in three projects using hFT having progressed as at 31 December. An additional three projects using hESC were approved in 2018, resulting in nine projects using 13 different hESC lines or derived cells having been approved to date.

Animal research

We are committed to helping the public understand the continuing need for animals in research, and our approach to replacing, reducing and refining our use of animals (the 3Rs).

We share our 3Rs advances externally through presentations at international conferences and workshops, and contribute to the work of organisations and societies supporting the 3Rs around the world. Our Chief Veterinary Officer leads the Council for Science and Animal Welfare (C-SAW), which is the governance and oversight body for the use of animals in research and development, providing assurance to senior leaders on our responsible use of animals. C-SAW drives initiatives on the 3Rs, openness about our use of animals, and promotes a culture of care in the way we conduct our research. For example, C-SAW runs an annual global awards scheme recognising excellence in the 3Rs, achievements in openness about the use of animals and the best examples of a caring research culture. Each year, one of the 3Rs award winners is further selected to receive a CEO Award for the 3Rs. In 2018, this went to a group who achieved a six-fold reduction in the numbers of mice needed for particular studies by the application of novel experimental design. C-SAW also promotes global learning and continuing professional development opportunities for employees working with animals and provides general information and education opportunities both within and outside AstraZeneca.

Animal research use varies depending on many interrelated factors, including our amount of pre-clinical research, the nature and complexity of the diseases under investigation and regulatory requirements. We believe that without our active commitment to the 3Rs, our animal use would be much greater. In 2018, animals were used for in-house studies 121,823[1] times (2017: 131,615). In addition, animals were used on our behalf for CRO studies 29,853 times (2017: 28,545). In total, over 97% were rodents or fish.

Technology has not yet advanced to the stage where animal use can be eliminated, and animal studies therefore remain a small, but necessary, part of the process of developing new drugs. We are alert to the issues around the use of animals and are working constantly to ensure our animal studies are properly justified, conducted and reported.

[1] 2018 figure includes some animals used only for breeding.

For more information, see our 2018 Sustainability Report available on our website, www.astrazeneca.com/sustainability.

Ethical supply chain management

Every employee and contractor who sources goods and services on behalf of AstraZeneca is expected to follow responsible business processes, which are embedded into our newly updated Global Standard for the Procurement of Goods and Services. All our procurement professionals receive detailed training on responsible procurement.

Our ethical standards are integral to our procurement and partnering activities and we monitor compliance through assessments and improvement programmes. We work only with those suppliers whose standards of ethical behaviour are consistent with our own. We will not use suppliers who are unable to meet our standards. Our Global Standard Expectation of Third Parties is published on our website, www.astrazeneca.com/sustainability.

To achieve this, we have an established process for third party risk management. This process assesses risk based upon defined criteria. These include risks related to bribery and corruption, data privacy, the environment

12,967

12,967 assessments of suppliers in 2018 to ensure they meet our ethical standards

$19m

$19 million committed to resource efficiency projects at our manufacturing and R&D sites in 2018

"We follow the science to protect the planet by managing our impact on the environment across all our operations."

and wages. Each step of the process provides an additional level of assessment, and we conduct more detailed assessments on those relationships identified as higher risk. Through this risk-mitigation process, we seek to better understand the partner's risk approach and seek to ensure the partner understands and can meet our standards.

We conducted a total of 12,967 assessments in 2018, taking our total number of assessments to 27,257 since we established this process in May 2014. Of the assessments undertaken in 2018, 3,390 were in the Asia Pacific region, 4,035 in Europe and 3,965 in the Americas. The remaining 1,577 assessments relate to global suppliers and those based in the Middle East and Africa.

In 2018, we conducted 45 audits on high-risk suppliers (external manufacturing partners), seeking to ensure that they employ appropriate practices and controls. Eighty six percent of these suppliers met our expectations, with a further 14% implementing improvement plans to address minor instances of non-compliance. Through our due diligence process, we rejected seven suppliers because of reputational concerns due to high anti-bribery/anti-corruption risk.

3. Protecting the environment

We follow the science to protect the planet by managing our impact on the environment across all our operations. Our Code of Ethics is the overarching document for our environmental management system. It applies to all functions and locations and is supported by global standards and procedures that establish mandatory requirements in key risk areas. We monitor and manage performance through comprehensive assurance programmes that include performance reporting and internal auditing. We are on track to deliver our 2016 to 2025 natural resources targets.

Our 2018 targets (against a 2015 baseline) included:

> reducing our operational greenhouse gas (GHG) footprint in line with our approved Science Based Target
> limiting the increase in our energy consumption to no more than 2% to 1,841 GWh
> limiting the increase in our waste generation to less than 7% to 32,811 tonnes
> reducing water use by 7% to 4.03 million m^3.

The table opposite provides data on our global GHG emissions, energy use, waste production and water consumption for 2018. The data coverage includes 100% of our owned and controlled sites globally. Regular review of the data is carried out to ensure accuracy and consistency. This has led to changes in the data for previous years. To support the achievement of our targets, a resource efficiency capital fund has been in place since 2015 to invest in projects at sites. In 2018, $19 million (2017: $19 million) was committed to resource efficiency projects at our manufacturing and R&D sites, and a further $15 million has been committed for 2019.

Greenhouse gas

We are working to reduce our GHG emissions by, among other things, investment in improving energy and fuel efficiency and pursuing lower-carbon alternatives to fossil fuels, utilising a hierarchy approach of avoiding emissions where possible, reducing emissions from necessary activities, and substituting our energy sources for lower carbon alternatives. During 2018, we made progress towards our verified science-based targets for Scope 1 and Scope 2 emissions through increased fuel efficiency of our commercial sales fleet and procurement of electricity from certified renewable sources increasing to represent 69% of total electricity imports. Our total Scope 1 and Scope 2 emissions have been reduced by 31% from our 2015 baseline. We have continued to make progress on our science-based targets for Scope 3 emission sources through continued achievement in switching freighting of goods from air to sea and improved accounting of our Scope 3 footprint that will lead to future efficiency improvements. Including emissions from patient use of our inhaler therapies, our operational GHG footprint totalled 1,769,110 metric tonnes in 2018, a reduction of 0.4% from our 2015 baseline.

For more information on our pressurised metered dose inhaler (pMDI) therapies, see the Product environmental stewardship section opposite.

Energy use

To reduce GHG emissions, we recognise the need to reduce our demand for energy in the first instance, maximise the efficiency of the energy we do use and, where feasible, substitute our energy use with renewable sources. Due to anticipated net increase in activity across our site network in 2018, we aimed to limit increases in total energy consumption to 2% above our 2015 baseline. Over the same period, we completed seven in-depth energy audits to identify new opportunities for energy efficiency that will be implemented over the next three years. In 2018, our energy use was 1,854 GWh, an increase of 3%. We have made further progress on our target to use 100% renewable power by 2025. In 2018, we used certified zero emission power equivalent to 61% of total power consumption, including 3,358 MWh of renewable power generated on our sites.

For more information on GHG emissions reporting, see Sustainability: supplementary information on page 231.

Operational greenhouse gas footprint emissions (tonnes CO_2e)[1]

2018	**1,769,110**
2017	1,705,047
2016	1,683,959
2015	1,776,508

1,769,110 tonnes CO_2e

Energy consumption (MWh)[1]

2018	**1,853,813**
2017	1,745,547
2016	1,785,357
2015	1,805,236

1,853,813 MWh

% total energy from renewables[1]
2018 29%
2017 27%
2016 25%
2015 6%

Waste production (tonnes)

2018	**31,500**
2017	31,063
2016	31,791
2015	30,665

31,500 tonnes

Water use (million m³)

2018	**4.01**
2017	3.89
2016	4.02
2015	4.34

4.01 million m³

[1] Regular review of the data is carried out to ensure accuracy and consistency. This has led to changes in the data from previous years. The majority of adjustments made are not material individually, except for business air travel (new data supplier, leading to restated baseline) and product use phase (recalculated using improved life-cycle emissions data). The data quoted in this Annual Report are generated from the revised data.

Waste

Waste management is another key aspect of our commitment to minimise environmental impact. Due to anticipated growing activity across our site network in 2018, we aimed to limit increases in our waste volumes to a 7% increase from our 2015 baseline. In 2018, our total waste was 31,500 metric tonnes, a 3% increase on 2015. As waste generation is linked to production volumes, our waste reduction ambitions are going to be challenged as our business grows. However, we are focusing on processes to boost our operational efficiency and investing in waste reduction projects to help us reach our target to reduce waste generation by 10% by 2025. While waste prevention is an essential goal, we seek to maximise treatment by material recycling and avoiding landfill disposal when prevention is impractical.

Water

We recognise the need to use water responsibly and, where possible, to minimise water use in our facilities. In 2018, we targeted a 7% reduction from our 2015 water use. In 2018, our water footprint was 4.01 million m³, an 8% reduction. Water reduction and reuse projects throughout our site network have improved the efficiency of water use across our operations. Our major sites and those in water-stressed areas work to Water Conservation Plans to ensure we are managing our water risks and to facilitate sharing of best practice in water stewardship around our site network.

Product environmental stewardship

We are committed to ensuring effective environmental management of our products from pre-launch through to product end-of-life. We work at all stages of a medicine's life-cycle from the design of API production and formulation processes, devices and packaging through distribution, patient use and final disposal.

As part of our progress towards our 2025 environmental targets, our 2018 targets included:

> Safe API discharges for AstraZeneca sites (100%) and globally managed first tier suppliers (>90%). Target met – safe API discharges confirmed.

Our pMDI therapies rely on hydrofluoroalkane (HFA) propellants, which are emitted during use and disposal, and contribute to our Scope 3 GHG footprint. While HFAs have no ozone depletion potential and a third or less of the global warming potential than the chlorofluorocarbons they replaced, they are still potent greenhouse gases. During 2018, we initiated a project spanning all key functions in the business to investigate options available from an environmental, technical, regulatory, medical and commercial viewpoint. The environmental review includes life-cycle assessment (LCA) of current products and potential options, ecotoxicity and fate studies of alternative propellants and an initial pilot study for pMDI take-back and recycling programmes. It is imperative that decisions to address the product use phase GHG footprint do not substitute the climate impact for another environmental impact.

Pharmaceuticals in the environment

We aim to lead our industry in understanding and mitigating the effects of pharmaceuticals in the environment (PIE). An estimated 98% of pharmaceuticals get into the environment as a result of patient use (excretion or improper disposal). While API discharge from production is only a small proportion of the environmental burden, it is the part we as an industry can deal with directly. We manage the manufacturing discharge of our APIs in a responsible manner to ensure that we do not exceed the safe discharge standards set for our own manufacturing sites and those of key suppliers. We review compliance with these safe discharge standards annually. Using a concept called 'ecopharmacovigilance', we review emerging science and literature for new information that might change the way we assess and manage any environmental risks associated with our products through patient use and API production. A thorough assessment of the environmental risks resulting from the patient use of all our APIs has indicated that all our medicines currently pose low or insignificant environmental risk.

We also conduct collaborative research to understand the fate, behaviour and impact of pharmaceuticals on the environment. In 2018, we co-authored 21 peer-reviewed publications to enhance our knowledge of the risks associated with this emerging issue.

As part of our progress towards our 2025 environmental targets, our 2018 targets included:

> management of PIE through our ecopharmacovigilance programme. Target met – programme delivered.

Further information on our efforts in this area, including environmental risk assessment data for our medicines, is available on our website, www.astrazeneca.com/sustainability/environmental-sustainability.

Community investment

Wherever we work in the world, we aim to make a positive impact on our communities. Our Global Standard on Contributions encompasses community investment and provides guidance to ensure a consistent, transparent and ethical approach around the world, based on local need. Our activities are focused on healthcare in the community and supporting science education. They include financial and non-financial contributions. In 2018, we gave more than $57 million (2017: $25 million) through our community investment activities to more than 1,000 non-profit organisations in 70 countries. The increase reflects a change in practice with more large multi-year agreements with payments being made in the first year of the agreement. The amount includes more than $17.5 million (2017: $4 million) for product donations that were given in support of public health needs and disaster relief. The increase reflects changes in the volume and mix of product donated. In addition to these community investments, we also donated more than $686 million (2017: $401 million) of medicines in connection with patient assistance programmes around the world, the largest of which is our AZ&Me programme in the US.

For more information about AZ&Me, see page 31.

Our global disaster relief partner is the British Red Cross. In 2018, we entered into a two-year partnership that will support humanitarian aid to people affected by armed conflict in Northern Nigeria. Our global product donation partners are Americares, Direct Relief International and Health Partners International of Canada.

In 2018, we launched the Step Up! Young Health Global Grants Programme. Designed to complement our work in the field of adolescent health and NCD prevention, this programme offered grants of up to $10,000 to non-profit organisations that are innovating to improve the health and wellbeing of young people. A total of $160,375 of funding was committed through this programme in 2018 for 17 projects in 14 countries.

We continue to support *Connections for Cardiovascular Health*℠, a programme of the AstraZeneca HealthCare Foundation that was launched in 2010 to address heart health in the US. In 2018, the AstraZeneca HealthCare Foundation provided $1.16 million in grants to 11 non-profit organisations for programmes that aim to help prevent, better manage and reduce cardiovascular disease.

Making a positive impact on our communities is also about volunteering. We encourage our employees to volunteer and support their efforts with one day's leave for community service. In 2018, our employees volunteered more than 39,000 hours on community projects in countries around the world.

For more information on the Step Up! Young Health Global Grants Programme, visit www.younghealthprogrammeyhp.com.

For more information on the AstraZeneca HealthCare Foundation's *Connections for Cardiovascular Health*℠ programme, visit www.astrazeneca-us.com/foundation.

For more information on the AstraZeneca HealthCare Foundation, see the Glossary on page 240.

Young Health Programme

Non-communicable disease (NCD) prevention among young people continued to be an area of focus as we mark the ninth year of our award-winning Young Health Programme (YHP). Despite the fact that more than two thirds of premature deaths from NCDs can be linked to behaviours that first began in adolescence, young people and their health continues to be an under-recognised, under-served and under-researched component of the global health agenda. In 2018, we reached nearly 335,000 young people with health information on NCDs and risk behaviours and trained more than 5,500 peer educators and healthcare workers. In partnership with local governmental and non-governmental groups, we launched new programmes in Indonesia, Serbia, Turkey and Australia and approved the development of new programmes in Vietnam, Myanmar, Mexico and Panama. This brings the total number of developing and active YHP initiatives to 20.

We supported our partners, NCD Child and Plan International, as they advocated for the inclusion of adolescent health and NCD prevention in the Political Declaration on NCDs and at the United Nation's Third High Level Meeting on NCDs. We invested in new research on adolescent risk behaviours, policy recommendations and health economic analyses to support the argument for additional investment in and attention to NCD prevention among young people. We continued to mentor and support the development of young global health leaders by sending a delegation of 20 young people to the One Young World Summit in The Hague, Netherlands.

YHP was named Community Investment Program of the Year by Ethical Corporation's 2018 Responsible Business Awards.

Further information on YHP can be found on its website, www.younghealthprogrammeyhp.com.

Learn more in our 2018 Sustainability Report on www.astrazeneca.com/sustainability.

Donation programmes

In some countries, such as the US, where many individuals remain without insurance and cannot afford our medications, we offer a free drug patient assistance programme – AZ&Me – for qualifying patients. In other countries with evolving health systems, we partner to address challenges in access with a combination of donated products and financial support to build capacity and support patient needs. In Cambodia, since 2010, our partnership with Americares and the Sihanouk Hospital Centre of Hope (SHCH) has supported the Cambodia Breast Cancer Initiative. The partnership aims to strengthen existing treatment services while expanding in scale to reach additional patients. In 2018, the programme screened 963 new patients; provided information on early detection and screening to more than 14,700 individuals; diagnosed 93 cases of breast cancer and continued to treat 661 patients who were previously diagnosed; and administered more than 24,000 units of free AstraZeneca medicines to post-menopausal breast cancer patients in the SHCH's treatment cohort.

For more information about AZ&Me, see page 31.

Non-Financial Information Statement

Under sections 414CA and 414CB of the Companies Act 2006, as introduced by the Companies, Partnerships and Groups (Accounts and Non-Financial Reporting) Regulations 2016, AstraZeneca is required to include, in its Strategic Report, a non-financial statement containing certain information. As required by the Regulations, the Strategic Report contains information on the following matters:

- Environmental matters on pages 46-47 and page 231
- Employees from page 38
- Social matters from page 42
- Respect for human rights on page 41
- Anti-corruption and anti-bribery matters from page 43

References to our policies, due diligence processes and information on how we are performing against various measures in these areas, are contained throughout the Strategic Report. Information on the Group's Principal Risks are included in Risk Overview from page 70 and information on the non-financial key performance indicators relevant to our business is included in Key Performance Indicators from page 20. A description of our business model is contained in Business model and life-cycle of a medicine from page 8.

There is a critical unmet need in the treatment of advanced ovarian cancer: only 20% of women will be cured and more than 70% will relapse within three years following their initial therapy. The best opportunity to achieve sustained remission, with potential for a cure, is to treat patients when they are newly diagnosed. However, current treatment options only provide a modest improvement in time to relapse. Once a patient relapses their disease is considered incurable and, for the majority of women, they go on to receive multiple lines of treatment.

By using *Lynparza* maintenance therapy earlier in the treatment pathway, the SOLO-1 trial results show that 60% of newly-diagnosed patients with a BRCA mutation remain progression-free at three years compared to 27% of patients receiving placebo. At 41 months, the median progression-free survival (PFS – see Glossary on page 241) had not been reached for patients treated with *Lynparza*, compared to 13.8 months for patients treated with placebo, indicating that there may be a group of patients who continue to remain progression-free for a long time or, perhaps, are cured.

Since the initial approval of *Lynparza* four years ago, the ovarian cancer and overall PARP inhibitor environment has become increasingly competitive but, with SOLO-1, AstraZeneca and MSD have the potential to transform the standard of care for women with advanced BRCA-mutated ovarian cancer, while reinforcing the importance of testing for BRCA mutations at the time of diagnosis.

Science *can* help find a cure for ovarian cancer

20%
Only 20% of women will be cured of ovarian cancer

>70%
will relapse within three years following their initial therapy

A portfolio of DNA damage response inhibitors that selectively kill cancer cells while minimising the impact on normal cells.

Oncology

Our ambition is to push the boundaries of science to change the practice of medicine, transform the lives of patients living with cancer, and ultimately eliminate cancer as a cause of death. To do this, we focus on R&D and on our commercial capabilities to deliver a new generation of medicines that have the potential to redefine the treatment of cancer.

Part of AstraZeneca's antibody-drug conjugate scientific platform to target specific leukaemia cells.

Unmet medical need and world market

> Cancer is the second leading cause of death globally.
> Lung cancer has the highest cancer mortality rate, responsible for the deaths of 1.7 million people worldwide in 2018, followed by colorectal, stomach, liver and breast cancer.
> Breast cancer is among the most common types of cancer, affecting 4.6 million people worldwide. Other common cancers include prostate and ovarian cancer.

Estimated annual cancer cases (m)

1.7m

Lung cancer was responsible for the deaths of 1.7 million people in 2018.

70%

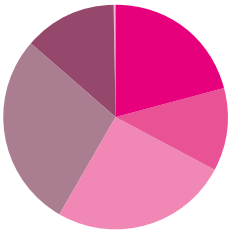
Approximately 70% of the world's cancer deaths occur in low- and middle-income countries.

Therapy area world market

(MAT/Q3/18)

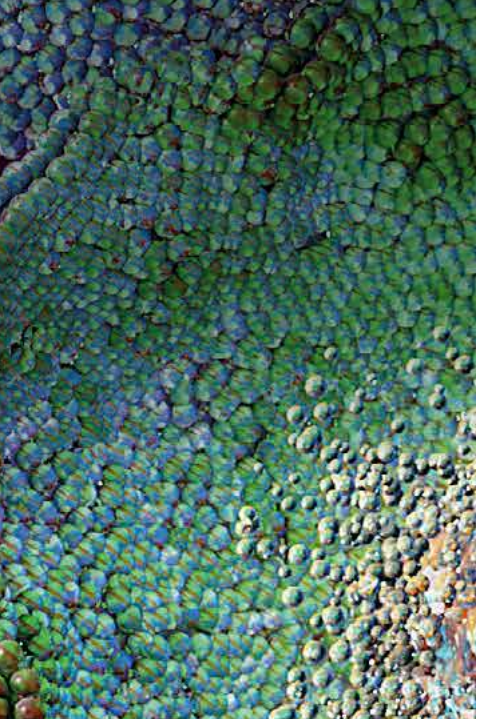
$106.6bn

Annual worldwide market value



- Chemotherapy $22.5bn
- Hormonal therapies $12.5bn
- Monoclonal antibodies (mAbs) $27.3bn
- Small molecule targeted agents $30.1bn
- Immune checkpoint inhibitors $14.2bn
- Other oncology therapies $0.1bn

Source: IQVIA.
AstraZeneca focuses on specific segments within this overall therapy area market.



Key marketed products and revenues 2018

The continued renewal of our commercial portfolio, the regulatory approvals of new indications for several established brands, and the rapid geographic expansion of our launches drove Oncology performance in 2018.

Oncology revenue

$6,028m

29% of total

2017: $4,024m

2016: $3,383m

Product	Disease area	Revenue	Commentary
Tagrisso (osimertinib)	Lung cancer	↑ $1,860m, up 95% (93% at CER)	Approved in more than 55 countries, including the US, Japan and EU, for 1st line EGFRm advanced non-small cell lung cancer (NSCLC), and more than 80 countries, including the US, Japan, China and the EU, for 2nd line use in patients with EGFRm T790M mutation-positive advanced NSCLC.
Lynparza (olaparib)	Ovarian cancer Breast cancer	↑ $647m, up 118% (116% at CER)	Approved in more than 60 countries for advanced ovarian cancer and approved in the US and Japan for metastatic breast cancer.
Imfinzi (durvalumab)	Lung cancer Bladder cancer	n/m $633m, movement n/m	Approved in more than 40 countries, including the US, EU and Japan, for locally advanced, unresectable, stage 3 NSCLC and in the US, Canada, Brazil, Israel, Australia, Hong Kong, the United Arab Emirates and India for locally advanced or metastatic urothelial carcinoma.
Calquence (acalabrutinib)	Mantle cell lymphoma (MCL)	n/m $62m, movement n/m	Approved in the US, the United Arab Emirates and Brazil for previously treated MCL.
Lumoxiti (moxetumomab pasudotox-tdfk)	Hairy cell leukaemia (HCL)		Approved in the US for ≥3rd line relapsed or refractory HCL. In 2018, the commercialisation rights of *Lumoxiti* were licensed to Innate Pharma for the US and EU.
Legacy			
Iressa (gefitinib)	Lung cancer	↓ $518m, down 2% (4% at CER)	
Faslodex (fulvestrant)	Breast cancer	↑ $1,028m, up 9% (9% at CER)	Approved in combination with CDK4/6 inhibitors.
Zoladex (goserelin acetate implant)	Prostate cancer Breast cancer	↑ $752m, up 2% (2% at CER)	
Arimidex (anastrozole)	Breast cancer	↓ $212m, down 2% (3% at CER)	
Casodex/Cosudex (bicalutamide)	Prostate cancer	↓ $201m, down 7% (8% at CER)	
Others		↔ $115m, up 1% (down 1% at CER)	

Full product information from page 217.

Our strategy for Oncology

In 2018, we divided our Oncology business into five franchises that reflect both our commercial priorities and our key scientific platforms:

> *Tagrisso* and tumour drivers and resistance mechanisms
> *Imfinzi* and immuno-oncology
> *Lynparza* and DNA damage response (DDR)
> *Calquence* and haematology
> Mature portfolio

These franchises enable us to best deliver against four strategic priorities we have embraced in order to achieve our ambition of eliminating cancer as a cause of death.

1. Focus research on four scientific platforms: Our broad pipeline of next-generation medicines is aimed at expanding our treatment options for solid tumours and haematological cancers. We are exploring several monotherapy and combination approaches across four scientific platforms:

> **Tumour drivers and resistance:** Developing therapies that target specific molecular mutations to attack cancer cells.
> **Immuno-oncology:** Using the body's immune system to help fight cancer.
> **DNA damage response:** Targeting the DNA repair process to block tumour cells' ability to reproduce.
> **Antibody-drug conjugates:** Arming antibodies with cancer-killing agents for specific tumour targeting.

2. Focus on early stages of disease and relapsed or refractory patients: To move the current cancer treatment paradigm, we recognise we must both identify and treat patients earlier in their disease progression when there is a possibility of cure, and also improve the treatment of relapsed or refractory patients to extend survival and deliver the most transformative outcomes.

3. Lead precision medicine in the most prevalent and deadly tumour types: On our path to eliminating cancer as a cause of death, we have set ourselves the goal of improving five-year survival in tumour types where mortality remains high, such as ovarian and NSCLC. We also continue to concentrate on biomarker-driven indications where the benefits to patient populations are tangible and significant.

4. Leverage our global footprint: To deliver these treatment-changing solutions to as many patients in need as possible, we are building capacity across all geographies. In addition, through our Oncology Business Unit we are increasing focus and improving response time in key markets such as the US, UK, Italy, France, Germany, Spain, Japan and China.

2018 pipeline highlights

Our robust pipeline includes 83 projects in various stages of clinical development, from recently approved products to earlier-stage molecules in clinical trials.

In 2018, we presented new clinical data at major medical congresses and secured multiple regulatory milestones, reflecting our continuing investment in oncology as one of our key growth drivers. Highlights include:

> Important new data from the pivotal Phase III PACIFIC trials in NSCLC, demonstrating a statistically significant benefit in overall survival with *Imfinzi*.
> Results from the Phase III SOLO-1 trial, investigating *Lynparza* in 1st line maintenance therapy for advanced ovarian cancer.
> Results from the Phase III MYSTIC and EAGLE trials exploring *Imfinzi* as monotherapy or in combination with tremelimumab respectively in 1st line setting of metastatic NSCLC and in recurrent or metastatic head and neck squamous cell carcinoma (HNSCC).

Full details are given in the Development Pipeline from page 212 and highlights from the progress our Oncology pipeline made in 2018 against our KPIs are shown below.

Life-cycle phases – R&D

New molecular entity (NME) Phase II starts/progressions

Over 20 clinical trials in Phase II explore combination and monotherapy approaches for tumours where high unmet medical need persists, like head and neck, gastric, breast, lung and ovarian cancers.

Product	Cancer type
AZD2811	Solid tumours
Imfinzi + *Lynparza*	Bladder cancer (BAYOU)
Imfinzi + monalizumab	Solid tumours
Oleclumab + *Imfinzi*	Solid tumours

NME and major life-cycle management (LCM) positive Phase III investment decisions

Life-cycle management is critical to realising the full potential of our medicines and establishing sustainable franchises. In 2018, we started 10 new Phase III trials bringing the total number of ongoing Phase III trials to 29.

Product	Cancer type
Imfinzi + CTx	Muscle invasive bladder cancer (NIAGARA)
Imfinzi + CTx	Neoadjuvant NSCLC (AEGEAN)
Imfinzi + TACE	Locoregional hepatocellular carcinoma (HCC) concurrent (EMERALD-1)
Imfinzi + tremelimumab	1st line limited disease small cell lung cancer (SCLC) (ADRIATIC)
Imfinzi + tremelimumab + CTx	1st line urothelial cancer (NILE)
Lynparza + abiraterone	All-comers 1st line metastatic castration resistant prostate cancer (PROpel)
Tagrisso	EGFRm leptomeningeal cancer (BLOSSOM)

Plus eight projects where investment decisions have been made but clinical trials have yet to start.

NME and major LCM regional submissions

In 2018, positive pivotal trial data from our oncology pipeline fuelled regulatory submissions. We received three Orphan Drug designations for *Lynparza* in pancreatic cancer (POLO) in the US and selumetinib in neurofibromatosis type 1 (SPRINT) in the US and EU, and benefited from three Priority Reviews.

Product	Cancer type	Region
Imfinzi	Stage 3 NSCLC (PACIFIC)	China
Lumoxiti	3rd line HCL (PLAIT)	US
Lynparza	1st line ovarian cancer (SOLO-1)	US, EU, China, Japan
Lynparza	gBRCA metastatic breast cancer (OlympiAD)	EU
Tagrisso	1st line NSCLC (FLAURA)	China

Life-cycle phases – approvals

NME and major LCM regional approvals

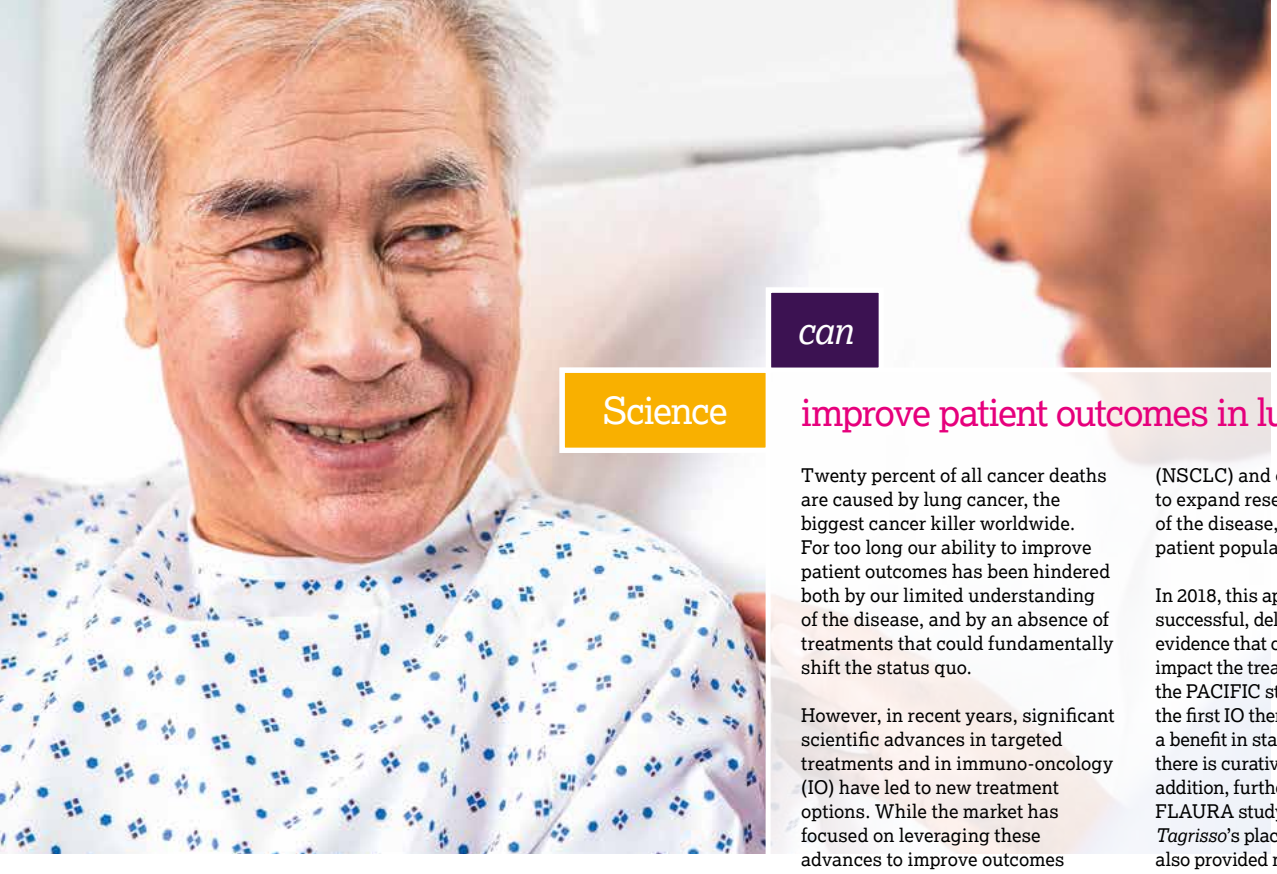
In the US, EU, Japan and China, we secured 13 new regional approvals in 2018, underlining our commitment to providing patients with access to life-changing medicines globally.

Product	Cancer type	Region
Imfinzi	Unresectable stage 3 NSCLC (PACIFIC)	US, Japan, EU
Lumoxiti	3rd line HCL	US
Lynparza	1st line ovarian cancer (SOLO-1)	US
Lynparza	2nd line ovarian cancer (SOLO-2)	Japan, EU, China
Lynparza	gBRCA metastatic breast cancer (OlympiAD)	US, Japan
Tagrisso	1st line NSCLC (FLAURA)	US, EU, Japan

Discontinued projects

Product	Cancer type	Reason
Calquence + vistusertib	BTK + mTor haematalogical tumours	Safety/efficacy
Imfinzi + tremelimumab	PD-L1 + CTLA-4 3rd line NSCLC (ARCTIC)	Safety/efficacy
Imfinzi + tremelimumab	2nd line HNSCC (EAGLE)	Safety/efficacy
Imfinzi + tremelimumab	1st line NSCLC (MYSTIC)	Safety/efficacy
Imfinzi or *Imfinzi* + (tremelimumab or danvatirsen)	Diffuse large B-cell lymphoma (DLBCL)	Safety/efficacy
Imfinzi + MEDI0562	Solid tumours	Safety/efficacy
Imfinzi + MEDI9197	Solid tumours	Safety/efficacy
MEDI-565	CEA BITE GI tumours	Safety/efficacy
MEDI0562	Solid tumours	Safety/efficacy
MEDI1873	Solid tumours	Strategic
MEDI4276	HER2 solid tumours	Safety/efficacy
MEDI9197	Solid tumours	Safety/efficacy
Selumetinib	Differentiated thyroid cancer (ASTRA)	Safety/efficacy
Tremelimumab + MEDI0562	Solid tumours	Safety/efficacy
Vistusertib	mTOR stage 1/2 solid tumours	Safety/efficacy

For more information on the life-cycle of a medicine, see page 9.



Science *can* improve patient outcomes in lung cancer

Twenty percent of all cancer deaths are caused by lung cancer, the biggest cancer killer worldwide. For too long our ability to improve patient outcomes has been hindered both by our limited understanding of the disease, and by an absence of treatments that could fundamentally shift the status quo.

However, in recent years, significant scientific advances in targeted treatments and in immuno-oncology (IO) have led to new treatment options. While the market has focused on leveraging these advances to improve outcomes for late-stage patients, we have leveraged our heritage in EGFRm non-small cell lung cancer (NSCLC) and our broad IO pipeline to expand research into earlier stages of the disease, and to emerging patient populations.

In 2018, this approach proved to be successful, delivering clinical evidence that could significantly impact the treatment of NSCLC. With the PACIFIC study, *Imfinzi* became the first IO therapy to demonstrate a benefit in stage 3 NSCLC where there is curative possibility. In addition, further data from the FLAURA study not only reaffirmed *Tagrisso*'s place in 1st line, but they also provided new insights into optimising treatment for metastatic EGFRm NSCLC, where five-year survival rates remain at less than 15%.

2018 review – strategy in action

Oncology is one of our main therapy areas and has a major role to play in our Return to Growth, with an aim of launching six new oncology medicines between 2014 and 2020.

In 2015 and 2016, we continued to build our oncology business by investing in a robust clinical development programme and by making strategic partnerships and acquisitions, such as acquiring a majority equity stake in Acerta Pharma to establish our footprint in haematology.

In 2017, we created the Oncology Business Unit (OBU) focused on eight key markets, with the aim of accelerating the uptake of our new medicines through strategic focus, quick decision making, and adequate investments.

In 2018, based on the commercial uptake of our new medicines, and the maturity of their late-stage clinical programmes, we organised the OBU into five franchises: *Tagrisso*, *Imfinzi*, *Lynparza*, *Calquence* and our mature portfolio.

Tagrisso and tumour drivers and resistance mechanisms

Tagrisso is our best-in-class, highly-selective, irreversible inhibitor of the activating sensitising EGFR mutation (EGFRm) and the resistance mutation T790M.

Our tumour drivers and resistance (TDR) mechanisms platform explores the inhibition of genetic disease drivers as a clinically validated approach to shrink tumours and improve progression-free survival (PFS) and overall survival (OS). Tumours, however, eventually develop resistance to these therapies. Our programmes seek to develop therapies that target resistance mechanisms and the mutations that cause cancer cells to proliferate.

In 2018, *Tagrisso* was approved for 1st line EGFRm advanced NSCLC, based on the positive results from the Phase III FLAURA trial. The approval was granted in the US in April, in the EU in June and in Japan in August.

By December 2018, it was approved in more than 55 countries for 1st line EGFRm advanced NSCLC, and in more than 80 countries for 2nd line use in patients with EGFRm T790M mutation-positive advanced NSCLC.

In October 2018, new data from the FLAURA Phase III trial presented at the European Society for Medical Oncology (ESMO) 2018 Congress provided insights on the resistance mechanisms observed after treatment with 1st line *Tagrisso* in patients with previously untreated EGFRm NSCLC who experienced disease progression during the trial period. As expected, there was no evidence of the acquired EGFR T790M mutation and the most frequently experienced resistance mechanisms – MET (mesenchymal epithelial transition factor) amplification and C797X mutations – were confirmed.

Based on these findings, we announced the initiation of ORCHARD, an open-label, multi-centre, multi-drug Phase II platform trial in patients with advanced NSCLC who have experienced disease progression following 1st line therapy with *Tagrisso*.

During 2018, we also confirmed our commitment to tackling earlier stages of EGFRm NSCLC with the ADAURA and LAURA clinical trials. ADAURA will assess the efficacy and safety of *Tagrisso* in EGFRm stage Ib-3A NSCLC, following complete tumour resection with or without adjuvant chemotherapy, and LAURA will assess the efficacy and safety of *Tagrisso* following chemoradiation in patients with stage 3 unresectable EGFRm NSCLC. Our next generation of TDR projects continued to progress in 2018:

> Savolitinib, a selective inhibitor of c-MET receptor tyrosine kinase, is being investigated in partnership with Chi-Med in combination with *Tagrisso* in EGFR mutated lung cancers which also have amplification of MET, a common resistance mechanism in patients progressing on *Tagrisso*. It is also being explored as monotherapy in NSCLC patients with MET Exon 14 skipping mutations, and in combination with *Imfinzi* in renal cancer.

> Selumetinib, an MEK inhibitor, part of the portfolio agreement with MSD, continued to be investigated in the SPRINT trial for neurofibromatosis type 1. Selumetinib was granted Orphan Drug designation in the US and Europe for this potential indication in 2018. Promising early combination data of novel ERK inhibitor AZD0364 and selumetinib in KRAS-mutated tumours was presented at the American Association for Cancer Research annual meeting in April 2018. However, in the second quarter of 2018, after the ASTRA trial failed to meet its primary endpoint, further Phase III development of selumetinib in thyroid cancer was discontinued.

> Capivasertib (AZD5363) had promising Phase II data presented at the American Society of Clinical Oncology (ASCO) conference in June 2018 showing an OS improvement in combination with paclitaxel in patients with 1st line metastatic triple negative breast cancer. Capivasertib is also in Phase II trials in ER+ breast cancer in combination with *Faslodex* and in prostate cancer in combination with enzalutamide.

Other agents in early development include: AZD9496 and AZD9833, selective oestrogen receptor degraders (SERD) in Phase I development for the treatment of oestrogen receptor positive (ER+) breast cancer; AZD5153, a bromodomain 4 inhibitor in Phase I for solid tumours; and AZD8186, an inhibitor of PI3 kinase β and δ in Phase II for solid tumours.

Imfinzi and immuno-oncology

Imfinzi, a human mAb that binds to PD-L1 and blocks the interaction of PD-L1 with PD-1 and CD80, is the cornerstone of our extensive IO programme. In 2018, it received approval for locally-advanced, unresectable, stage 3 NSCLC in more than 40 countries, including the US, EU and Japan. It also secured approval for locally-advanced or metastatic urothelial carcinoma (bladder cancer) in Canada, Brazil, Israel, Hong Kong, Australia, the United Arab Emirates and India.

Immuno-oncology (IO) is a promising therapeutic approach that harnesses the patient's own immune system to help fight cancer. We aim to become scientific leaders in IO by identifying novel approaches that enhance the immune system's ability to fight cancer, both with IO medicines on their own, and in conjunction with other medicines.

In 2018, our comprehensive IO clinical programme continued to provide insights on the clinical potential of *Imfinzi* in a variety of different clinical settings, both as a monotherapy as well as in combination with chemotherapy and tremelimumab.

Early-stage NSCLC

In May 2018, we announced positive topline OS results for the Phase III PACIFIC trial of *Imfinzi* in patients with unresectable stage 3 NSCLC. Data that show *Imfinzi* reduced the risk of death by nearly one third were subsequently presented on 25 October during the Presidential Symposium of the International Association for the Study of Lung Cancer 19th World Conference on Lung Cancer. With the PACIFIC trial results, we are the first company to demonstrate the benefits of treating NSCLC patients with an immuno-therapy where curative intent is the treatment goal, ie before the disease has spread to multiple organs.

Lung cancer is a key area of focus for our IO portfolio and in 2018 we announced our commitment to investigate the full potential of *Imfinzi* in early-stage NSCLC with the Phase III ADJUVANT (BR.31), PACIFIC-2 and PACIFIC-5 trials:

> ADJUVANT will explore the benefits of treatment with *Imfinzi* following complete tumour resection.
> PACIFIC-2 will assess efficacy and safety of *Imfinzi* given concurrently with platinum-based chemotherapy radiation in stage 3 NSCLC patients.
> PACIFIC-5 will assess the efficacy and safety of *Imfinzi* as consolidation therapy in patients with locally-advanced, unresectable NSCLC.

Late-stage NSCLC

In April 2018, we announced the results of the Phase III ARCTIC trial exploring *Imfinzi* and tremelimumab in monotherapy or in combination in 3rd line locally-advanced or metastatic NSCLC. The data, presented on 22 October at the ESMO 2018 Congress, demonstrated that *Imfinzi* monotherapy provided a clinically meaningful reduction of the risk of death compared to chemotherapy in patients with PD-L1 high/positive tumours and that the combination did not significantly improve PFS or OS compared to chemotherapy in patients with PD-L1 low/negative tumours.

In November 2018, the final analysis of the MYSTIC trial showed that for patients with stage 4 (metastatic) NSCLC, whose tumours express PD-L1 on 25% or more of their cancer cells, *Imfinzi* monotherapy and the combination of *Imfinzi* plus tremelimumab did not meet the primary endpoints of improving OS compared to the current standard of care (SoC) chemotherapy. The results presented at the December ESMO-IO Congress showed that *Imfinzi* monotherapy demonstrated meaningful clinical activity in patients whose tumours express PD-L1 on 25% or more of their cancer cells, but this result did not meet statistical significance. The data support further analysis in exploratory subgroups, including blood tumour mutational burden (bTMB) analyses.

We also continued our efforts to explore ways to improve outcomes for patients who have relapsed or are diagnosed with metastatic disease. In this setting, *Imfinzi* is being investigated as a monotherapy and in combination with tremelimumab and/or chemotherapy in the PEARL, NEPTUNE and POSEIDON trials.

Beyond NSCLC

In December 2018, the final data from the EAGLE study showed *Imfinzi* monotherapy and the combination of *Imfinzi* plus tremelimumab did not meet the primary endpoints of improving OS compared to SoC chemotherapy in patients with recurrent or metastatic HNSCC who experienced disease progression following platinum-based chemotherapy. We continue to explore the potential of *Imfinzi* and tremelimumab in HNSCC in the ongoing KESTREL trial, in patients with 1st line recurrent or metastatic disease, with data expected in the first half of 2019. Our extensive IO programme also includes ongoing Phase III trials in small cell lung cancer (SCLC) with CASPIAN, in bladder cancer (POTOMAC, NIAGARA, DANUBE, NILE) and in hepatocellular carcinoma (HIMALAYA).

In addition to these major clinical trials, our IO pipeline, one of the largest in the industry, continued to progress:

> MEDI9447: In June 2018, data from the Phase I study of oleclumab (MEDI9447), targeting ecto-5'-nucleotidase (CD73), in combination with *Imfinzi* in advanced pancreatic cancer and colorectal cancer was presented at the ASCO annual meeting.
> AZD9150: In October 2018, data from the SCORES Phase II study in patients with 2nd line HNSCC showed encouraging tumour response rate for the combination of danvatirsen (AZD9150, STAT3 antisense oligonucleotide) with *Imfinzi*, including biopsy data showing modulation of the tumour microenvironment.
> Monalizumab: In October 2018, we announced a new agreement with Innate Pharma in which we will exercise our existing option to obtain full oncology rights to monalizumab, a first-in-class humanised anti-NKG2A antibody which has demonstrated positive Phase II results in head and neck cancer and presents opportunities in colorectal cancer and haematological malignancies as well. The agreement also provided us with access to Innate Pharma's anti-CD39 mAb, IPH5201, plus four additional IO molecules, increasing the breadth and depth of our IO portfolio.
> AZD4635, an Adenosine 2A receptor (A2AR) inhibitor is being explored as monotherapy and in combination with *Imfinzi* in solid tumours in Phase II trials. In addition, combination trials of AZD4635 with oleclumab (anti-CD73 Ab), and with oleclumab and *Imfinzi* are ongoing with the goal of testing increased adenosine axis blockade, a key immunosuppressive mechanism.
> MEDI0680, an anti-programmed cell death protein 1 (PD1) mAb that blocks interactions with PD1 and its ligands, is being investigated in combination with *Imfinzi* in a Phase II study to treat solid tumours.
> MEDI0457, a DNA vaccine against human papilloma virus (HPV) 16/18 is being investigated in combination with *Imfinzi* in a Phase II study in patients with HPV-associated head and neck tumours.
> Potential new products in Phase I include MEDI5752, a novel bispecific antibody designed to target dual checkpoints on immune cells, and MEDI5083 targeting CD40 receptor. These agents are in Phase I development for a range of solid tumours and have the potential for combination with other molecules in the portfolio, including *Imfinzi*.

Lynparza and DNA damage response

Lynparza is our best-in-class oral poly ADP ribose polymerase (PARP) inhibitor, the flagship of our DDR programme.

Our DNA damage response (DDR) platform exploits mechanisms that selectively damage tumour cell DNA to shrink tumours and improve Progression Free Survival (PFS) and Overall Survival (OS). Our market-leading programmes focus on multiple ways to identify and exploit vulnerabilities to kill the tumour cells, while minimising toxicity to the patient.

In 2018, *Lynparza* became the first and only PARP inhibitor approved beyond ovarian cancer for the treatment of germline BRCA-mutated (gBRCAm) HER2- metastatic breast cancer in the US and Japan. The US approval in January 2018 and the Japan approval in July 2018 were based on the Phase III OlympiAD trial which demonstrated the benefits of *Lynparza* over chemotherapy for patients with gBRCAm HER2- metastatic breast cancer.

2018 has been a significant year for *Lynparza* as it fully benefited from the global strategic oncology collaboration with MSD to co-develop and co-commercialise the product, both as a monotherapy and in combination with other medicines, for multiple cancer types. In addition, new market entries, the tablet formulation (now approved in all major regions) and new indications in advanced breast cancer and for a broad label in platinum-sensitive relapsed ovarian cancer regardless of BRCA status also expanded the medicine's availability to new patients. By December 2018, *Lynparza* had been approved in more than 60 countries.

In October 2018, the SOLO-1 Phase III trial data demonstrated the significant benefit of extending PFS much earlier in the patient journey, bringing the goal of long-term remission and cure in ovarian cancer even closer. The results of SOLO-1, presented as part of the Presidential Symposium at the ESMO 2018 Congress, and published simultaneously in the New England Journal of Medicine, showed that 60% of women with newly diagnosed advanced BRCA-mutated ovarian cancer treated with *Lynparza* for 1st line maintenance therapy remained progression-free at three years compared to 26.9% with placebo following platinum-based chemotherapy. At 41 months of follow-up, the median PFS was not reached in the *Lynparza* arm, while it had been reached at 13.8 months within the placebo arm. In December 2018, just a few weeks after the filing submission in the US, the FDA approved *Lynparza* for 1st line maintenance therapy in patients with BRCAm advanced ovarian cancer.

Our combination approach of *Lynparza* with other small molecules and biologics has significantly expanded in 2018. Cediranib, our orally administered multi-vascular endothelial growth factor receptor (VEGFR) inhibitor, is currently being tested in combination with *Lynparza* in the Phase IIb CONCERTO trial in patients with platinum-resistant recurrent ovarian cancer. Results are expected late in 2019. The DUO programme of *Lynparza* with *Imfinzi* has been extended to new potential indications (bladder cancer, NSCLC, ovarian cancer). Building on the PROfound Phase III trial that explores the efficacy and safety of *Lynparza* versus enzalutamide or abiraterone in subjects with metastatic castration-resistant prostate cancer, we started the Phase III PROpel trial that will assess the combination of *Lynparza* with abiraterone in 1st line metastatic castration-resistant prostate cancer.

In addition, from our extensive DDR portfolio, five other products continued to advance through early development. These include:

> AZD1775, a Wee1 inhibitor in Phase II development for ovarian and other solid tumours in combination with *Lynparza*, in combination with chemotherapy, and as monotherapy.
> AZD6738, an Ataxia Telangiectasia and Rad3 related (ATR) serine/threonine protein kinase inhibitor in Phase II development in combination with *Lynparza* for triple negative breast cancer, gastric cancer and other solid tumours. It is also being investigated in combination with *Calquence* in chronic lymphocytic leukaemia, and in combination with radiation therapy and chemotherapy, as well as a monotherapy.
> AZD2811 an Aurora Kinase inhibitor in development for Phase II in SCLC and acute myeloid leukaemia.
> AZD0156 and AZD1390, ATM inhibitors in Phase I for solid tumours.

Calquence and haematology

Calquence is our irreversible oral Bruton's tyrosine kinase (BTK) inhibitor.

The use of antibody-drug conjugates (ADC) is a clinically validated, highly potent approach that selectively targets cancer cells by combining innovative antibody engineering capabilities with cytotoxic drug molecules, to attack and kill the tumour while minimising toxicity to the patient.

In 2018, *Calquence* experienced encouraging early uptake in the US market following an October 2017 approval for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

In December 2018, at the American Society of Hematology congress, we presented the two-year follow-up results of the ACE-LY-004 Phase II trial showing sustained benefits for patients treated with *Calquence* in relapsed or refractory MCL. In addition, the updated results of the Phase I/II ACE-CL-001 trial, assessing the long-term safety and efficacy of *Calquence* in a cohort of previously untreated patients with chronic lymphocytic leukaemia (CLL), showed high response rates and demonstrated an acceptable safety profile. The median time on study was 33 months, with 91% of patients remaining on treatment with *Calquence* at the time of analysis.

In September 2018, *Lumoxiti* became the first medicine from our ADC scientific platform to get approved, and our fifth new oncology medicine since 2014.

Lumoxiti is a first-in-class anti-CD22 recombinant immunotoxin and the first new treatment option for hairy cell leukaemia (HCL) in over 20 years. It was approved in the US for the treatment of adult patients with relapsed or refractory HCL who have received at least two prior systemic therapies, including treatment with a purine nucleoside analogue.

In October 2018, we announced we will license the US commercial rights of *Lumoxiti* to Innate Pharma. Innate Pharma, with our support, will continue EU development and commercialisation, pending regulatory submission and approval. Innate Pharma will recognise revenues and co-commercialise *Lumoxiti* with us in the US and will take full responsibility by mid-2020. In addition, as part of the Innate Pharma agreement, we acquired monalizumab, a first-in-class, humanised anti-NKG2A antibody with a novel mode of action that is being investigated in several haematological malignancies and solid tumours.

In 2018, we also continued to advance our haematology early-phase clinical programme, with AZD5991, an MCL1 inhibitor, and AZD4753, a CDK9 inhibitor, both being investigated as part of our cell death programme, and ADCs, MEDI7247 and MEDI2228.

Mature portfolio

In 2018, our established oncology brands – *Faslodex*, *Zoladex* and *Iressa* – delivered good sales.

Faslodex continued to benefit from several 2017 1st line label extensions, based on the Phase III FALCON trial, for the treatment of post-menopausal women with oestrogen receptor positive, locally-advanced or metastatic breast cancer, not previously treated with endocrine therapy. In addition, the body of evidence supporting the use of *Faslodex* as a backbone therapy for use in combination in the treatment of advanced breast cancer continued to grow. All major CDK4/6 inhibitors, a new class of medicine for ER+/HER2- breast cancer, now include use with *Faslodex* in their labels.

Zoladex returned to value growth in 2018 following a six-year period of slowly declining sales across Europe and Japan. The growth was based on increased access to medical castration and ovarian suppression, as well as earlier detection and diagnosis in prostate and breast cancers, predominantly in China and the Emerging Markets.

Iressa sales declined slightly following generic entries in select markets and the initial uptake of *Tagrisso* in 1st line EGFRm advanced NSCLC.

Cardiovascular, Renal and Metabolism

Cardiovascular, renal and metabolic (CVRM) diseases combined are killing more than 20 million people each year. Yet, in many cases, each condition is managed in isolation. As science uncovers commonalities between these diseases and their associated complications, we aim to transform how CVRM diseases are understood and treated.

Nucleotide therapies – antiMRNA.

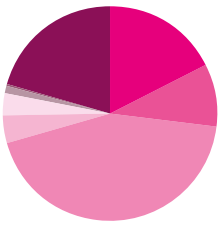
Unmet medical need and world market

20m
Number of deaths from CVRM diseases worldwide every year.

>93%
Proportion of people with type-2 diabetes that have at least one other CV, renal or metabolic condition.

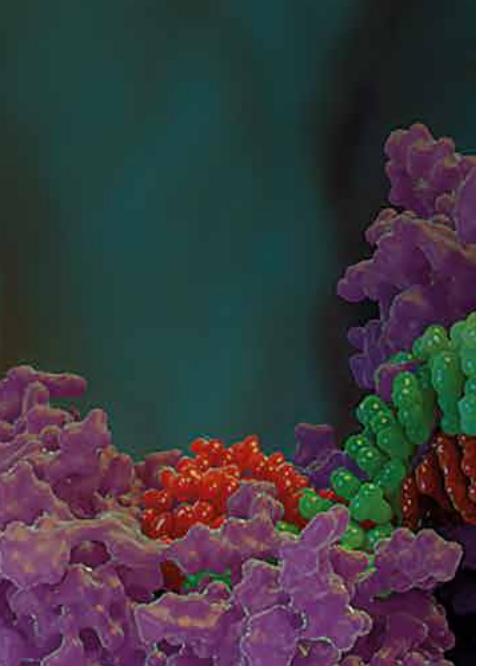
Therapy area world market
(MAT/Q3/18)

$183.8bn
Annual worldwide market value



- High blood pressure $33.3bn
- Abnormal levels of blood cholesterol $17.7bn
- Diabetes $82.5bn
- Thrombosis $7.7bn
- CKD $6.5bn
- CKD associated anaemia $2.0bn
- Hyperkalaemia $0.3bn
- Other CV $38.8bn

Source: IQVIA.
AstraZeneca focuses on specific segments within this overall therapy area market. CVRM total sales excludes partial double counting of hyperkalaemia and CKD associated anaemia market sales, which results from definitions overlapping with CKD and other CV.



Key marketed products and revenues 2018

CVRM supported AstraZeneca's Return to Growth by achieving blockbuster status for two of its main innovative medicines, *Farxiga* and *Brilinta*. Overall CVRM Product Sales were $6,710 million for 2018, down 8% on 2017 (8% at CER).

CVRM revenue

$6,710m

32% of total

2017: $7,266m

2016: $8,116m

Product	Disease area	Revenue	Commentary
Brilinta/Brilique (ticagrelor)	Acute coronary syndromes (ACS) and high-risk patients with history of myocardial infarction (MI)	↑ $1,321m, up 22% (21% at CER)	Approved in more than 100 countries for ACS and more than 60 countries for high-risk patients with history of heart attack; included in major guidelines. *Brilinta* delivered consistent quarter-over-quarter growth in 2018 in all regions.
Farxiga/ Forxiga (dapagliflozin)	Type-2 diabetes	↑ $1,391m, up 30% (30% at CER)	Approved in more than 90 countries to improve glycaemic control in adult patients with type-2 diabetes; included in major guidelines. It had a solid performance in 2018, driven by strong volume growth in a highly competitive market.
Onglyza (saxagliptin)	Type-2 diabetes	↓ $543m, down 11% (11% at CER)	Approved in more than 85 countries for the treatment of adults with type-2 diabetes; included in guidelines. *Onglyza* maintained a strong performance in 2018 in Emerging Markets, driven by China, while facing US price pressure.
Bydureon (exenatide XR injectable suspension)	Type-2 diabetes	↑ $584m, up 2% (1% at CER)	Approved in more than 70 countries to improve glycaemic control in adults with type-2 diabetes; included in major guidelines. In 2018, *Bydureon* continued launch progress with *BCise* in a highly dynamic GLP-1 class.
Byetta (exenatide injection)	Type-2 diabetes	↓ $126m, down 28% (28% at CER)	
Symlin (pramlintide acetate)	Diabetes	↓ $34m, down 29% (29% at CER)	
Legacy			
Crestor (rosuvastatin calcium)	Dyslipidaemia Hyper-cholesterolaemia	↓ $1,433m, down 39% (40% at CER)	Financial impact following the 2017 expiries in the US, EU and Japan receded in second half of 2018. Licensed from Shionogi. The extension of the global licence agreement with Shionogi for *Crestor* and the modification of the royalty structure became effective 1 January 2014.
Seloken/ Toprol-XL (metoprolol succinate)	Hypertension Heart failure Angina	↑ $712m, up 2% (4% at CER)	Divested rights in Europe to Recordati in May 2017. Divested US rights to Aralez effective 4 October 2016.
Atacand/ Atacand HCT/ *Atacand* Plus (candesartan cilexitil)	Hypertension Heart failure	↓ $260m, down 13% (12% at CER)	Divested rights to Cheplapharm in 28 European markets in July 2018. Licensed from Takeda Chemicals Industries Ltd.
Others		↓ $306m, down 11% (12% at CER)	

Our strategy for CVRM

CVRM diseases often coexist and many patients have symptoms or underlying pathologies associated with more than one CVRM disease. We are therefore focusing our efforts on the commonalities between these diseases and their underlying mechanisms to better understand how our portfolio might be used to address multiple risk factors or co-morbidities, and whether combinations of medicines might offer unique patient benefits.

We have a three-pronged science-driven strategy to address this extended CVRM risk:

1. Today, we are delivering life-changing results in the discrete core cardiovascular (CV) disease areas and their complications, with medicines already being used or in late-stage development:
> **Metabolic disease:** *Farxiga*, *Bydureon*, *Onglyza*, *Qtern*
> **Heart failure:** *Farxiga*
> **Renal:** *Lokelma*, roxadustat, *Farxiga*
> **Atherosclerosis:** *Brilinta*, *Epanova*, *Crestor*.

2. For the future, we are investing in science to demonstrate CV and mortality benefits by slowing the underlying progression of CV-related disease and protecting the organs of the CV system.

3. Ultimately, we are looking to do more than slow CV-related disease. We want to modify, or even halt, the natural course of the disease itself and regenerate organs.

Our new approach to care

Our aim is to improve care for CVRM patients by adopting a holistic approach to each patient and finding a seamless way in which to treat their diseases. We want to promote interdisciplinary collaboration among CV, renal and diabetes specialists and primary care physicians in order to change clinical practice and provide complete care for CVRM patients. Our approach is exemplified by:

1. Partnerships: We are actively seeking broader and stronger collaborations with respected academic institutions, research organisations, patient advocacy groups and healthcare companies.

2. Research: By taking risks, we can study compounds and treatments across diseases and combinations. We are seeking not only to understand the development and implications of each condition, but the interactions between two or more conditions, and how deterioration in one could adversely affect the others.

3. Real-world settings: Using data from real-world studies, we are better able to evaluate the connections between CVRM conditions and follow-up on patient outcome measures. For example, recent research collected multi-national real-world evidence (RWE) from more than 300,000 patients across six countries.

Therapy Area Review
Cardiovascular, Renal and Metabolism *continued*

2018 pipeline highlights

We have 29 potential medicines and medicine combinations in our pipeline, including small molecules and biologics, to address cardiac regeneration and individual conditions, such as chronic kidney disease (CKD), acute coronary syndromes (ACS), heart failure (HF) and non-alcoholic steatohepatitis (NASH) as well as in the broader CVRM disease context.

Full details are given in the Development Pipeline from page 212 and highlights from the progress our CVRM pipeline made in 2018 against our KPIs are shown below.

Life-cycle phases – R&D

New molecular entity (NME) Phase II starts/progressions

Our pioneering approach to exploring CV disease and heart regeneration saw advances in three Phase II clinical trials.

Product	Disease
AZD4831	Heart failure
AZD8601	CV disease
MEDI6012	CV disease

NME and major life-cycle management (LCM) positive Phase III investment decisions

We broadened our HF research to include a Phase III trial evaluating the effects of *Farxiga* on reducing CV death or worsening HF in patients with HF and a preserved ejection fraction (HFpEF), alongside functional and systematic studies for patients with both preserved and reduced ejection fraction (HFpEF/HFrEF).

Product	Disease
Farxiga/Forxiga	Heart failure (DELIVER)

Plus one project where investment decision has been made but clinical trial has yet to start.

NME and major LCM regional submissions

Our metabolism portfolio made significant regulatory strides, with five regulatory filings for our oral medicines and combination oral medicines, plus three major market data submissions from our injectables medicines.

Product	Disease	Region
Bydureon	Type-2 diabetes cardiovascular outcomes trial (CVOT) (EXSCEL)	EU, US, China
Bydureon BCise	Type-2 diabetes CVOT (DURATION programme harmonisation)	US
Bydureon BCise	Type-2 diabetes CVOT (EXSCEL)	US
Farxiga/Forxiga	Type-1 diabetes (DEPICT)	EU, Japan, US
Farxiga/Forxiga combination: saxagliptin + dapagliflozin + metformin	Type-2 diabetes	EU, US
Qtern	Dual add-on type-2 diabetes	US

Plus two projects where submissions have been made but have yet to be accepted.

Life-cycle phases – approvals

NME and major LCM regional approvals

We made important progress in advancing new molecules like *Lokelma* and roxadustat to address unmet needs of renal patients, as well as adding clinical evidence on clinically relevant CV outcomes alongside device enhancements of our established medicine, *Bydureon*, in the EU.

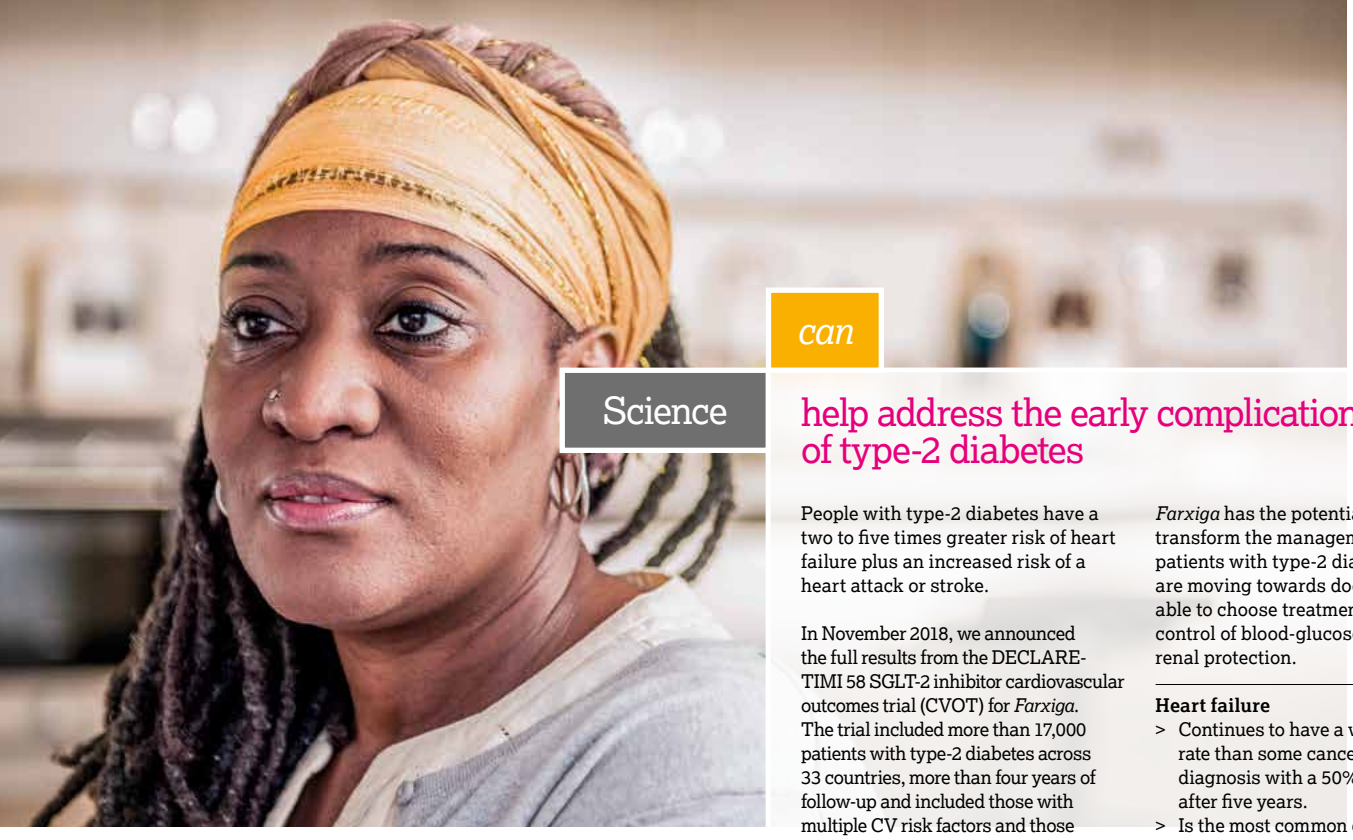
Product	Disease	Region
Bydureon	Add-on to insulin (DURATION 7)	US
Bydureon	CVOT (EXSCEL)	EU
Bydureon BCise	Type-2 diabetes weekly auto-injector	EU
Lokelma	Hyperkalaemia	EU, US
Roxadustat[1]	Chronic kidney disease anaemia	China

[1] Development and commercialisation collaboration with FibroGen in China. FibroGen holds the NDA.

Discontinued projects

Product	Disease	Reason
None	–	–

For more information on the life-cycle of a medicine, see page 9.



Science

can

help address the early complications of type-2 diabetes

People with type-2 diabetes have a two to five times greater risk of heart failure plus an increased risk of a heart attack or stroke.

In November 2018, we announced the full results from the DECLARE-TIMI 58 SGLT-2 inhibitor cardiovascular outcomes trial (CVOT) for *Farxiga*. The trial included more than 17,000 patients with type-2 diabetes across 33 countries, more than four years of follow-up and included those with multiple CV risk factors and those with established CV disease. This trial showed that *Farxiga* significantly reduced the risk of hospitalisation for heart failure or CV death by 17%. It also demonstrated a strong safety profile in a medicine class where some physicians have had concerns.

Farxiga has the potential to further transform the management of all patients with type-2 diabetes. We are moving towards doctors being able to choose treatment beyond control of blood-glucose to cardio-renal protection.

Heart failure

> Continues to have a worse survival rate than some cancers following diagnosis with a 50% survival rate after five years.
> Is the most common cause of hospitalisation in patients older than 65.
> Represents a considerable societal and economic burden: 25% of hospitalised patients are readmitted within 30 days and, at six months, readmission rates are almost 50%.

2018 review – strategy in action

We have adopted a unique CVRM strategy which includes investing in rigorous clinical programmes evaluating the use of our medicines in large patient populations in both Established and Emerging Markets. These trials include ambitious global randomised clinical trials (RCTs) that are as close as possible to clinical practice, as well as transformational RWE research.

> **Randomised clinical trials:** More than 60,000 patients are currently participating in our R&D-led CV trials at more than 6,000 sites worldwide. Our focus on diabetes research includes almost 50 clinical trials worldwide, with an enrolment target of 56,000 patients. These RCTs include the DapaCare Programme, OLYMPUS and ROCKIES, and THEMIS.
> **Real-world evidence data:** Our RWE studies include CVD-REAL and PRACTICAL, which both set out to deliver innovative data from large-scale settings.

Cardiovascular disease

Brilinta is an oral antiplatelet treatment for ACS, an umbrella term for sudden chest pain and other symptoms due to ischaemia (insufficient blood supply) to the heart, and for the long-term prevention of CV death, heart attack and stroke for patients with a history of heart attack.

In its ACS indication, *Brilinta* 90mg is approved in more than 100 countries, and is included in major ACS treatment guidelines globally. In its indication for the long-term prevention of CV death, heart attack and stroke for patients with a history of heart attack, since approval in 2016, *Brilinta* 60mg is now approved in over 70 countries.

We presented results of a new analysis of the PLATO trial at the American College of Cardiology meeting in March 2018, showing total mortality was reduced by 51% and CV death was reduced by 48%, when patients with ACS were treated with *Brilinta* within seven days prior to having heart bypass surgery, compared to patients treated with clopidogrel.

At the European Society of Cardiology (ESC) Congress, real-world data further reinforced the need to manage persistent ischaemic risk in patients, especially those with additional risk factors. PRECLUDE-2, an analysis of data from the ongoing SWEDEHEART quality registry involving more than 100,000 patients, found that the majority of post-myocardial infarction (MI) patients who have at least two CV disease risk factors, showed a marked but gradual increase in incidence of CV death, MI or stroke. The CV risk in patients with type-2 diabetes in the ATHENA study involving more than 300,000 patients demonstrated that diabetic patients who also have coronary artery disease, or who have experienced a prior heart attack or a stroke, are at greater risk of future CV death, heart attack and stroke than patients with just diabetes alone.

During the year, the first patient was enrolled into THALES, a new randomised, placebo-controlled Phase III dual antiplatelet therapy trial in stroke. This study forms part of PARTHENON, our largest ever CV outcomes programme involving more than 80,000 patients, within which THEMIS is the next major trial due to read out, studying the benefit of *Brilinta* for the prevention of CV events in patients with type-2 diabetes and coronary artery disease.

We continue to advance our large-scale CV outcomes trial (CVOT) (STRENGTH) to evaluate the safety and efficacy of *Epanova* on CV outcomes in combination with statin therapy for the treatment of patients with mixed dyslipidaemia who are at increased risk of CV disease. STRENGTH is the largest CVOT of any prescription omega-3 and completed enrolment in April 2017, with approximately 13,000 patients. Results are expected in 2020.

We are investigating the role of SGLT-2 inhibition in patients with heart failure as part of our DapaCare programme overleaf.

Crestor is approved in over 115 countries for the treatment of dyslipidaemia and hypercholesterolaemia (elevated cholesterol). The financial impact following the 2017 patent expiries in the US, EU and Japan receded in the second half of 2018. *Crestor* is now subject to generic competition in a number of markets.

In July 2018, we announced an agreement with Cheplapharm for the rights in Europe to *Atacand* (candesartan cilexetil) and *Atacand* Plus (fixed-dose combination of candesartan cilexetil and hydrochlorothiazide). *Atacand* is a prescription medicine for the treatment of heart failure and hypertension.

Renal diseases

Our ambition is to revolutionise the treatment of chronic kidney disease (CKD). We are investing in therapies across the continuum of CKD care, from disease modification during an early-stage diagnosis to managing life-threatening complications as patients progress to dialysis and end-stage renal disease.

Roxadustat is a first-in-class oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) that could transform the management of anaemia of CKD for patients both on dialysis and not on dialysis. We are collaborating in the development and commercialisation of roxadustat in the US, China and other markets not covered by an agreement between FibroGen and Astellas. In December 2018, we announced with FibroGen the approval of roxadustat by the National Medical Products Administration, marking the first time that a first-in-class medicine was approved first in China. Later in December 2018, we announced that the primary endpoints were met in OLYMPUS and ROCKIES, two AstraZeneca-sponsored trials within the global Phase III programme for roxadustat conducted by AstraZeneca, FibroGen and Astellas. These trials will contribute to a pooled safety analysis, which is anticipated during the first half of 2019 and will inform the US regulatory submission.

We are preparing for a broad launch of *Lokelma*, a best-in-class treatment for hyperkalaemia, in major markets. In March 2018 *Lokelma* was approved by the EMA and in May 2018, *Lokelma* was approved by the FDA. Subsequently, our focus was on ensuring broad availability to patients at launch in the US and Europe in 2019. In October 2018, we presented positive Phase III data from HARMONIZE Global, a *Lokelma* trial whose data will support future registrations in Japan, Russia, Korea and Taiwan.

We are exploring whether the medicines in our portfolio could modify the progression of CKD or offer organ protection as part of our DapaCare programme (see below).

Metabolic diseases

We are focused on redefining how diabetes is treated in unison with CV and renal diseases and the risk factors, harnessing complementary mechanisms of action and focusing on diverse populations with significant co-morbidities, such as CV disease (particularly heart failure), obesity, NASH, as well as diabetic nephropathy and CKD. Our global clinical research programmes seek to advance understanding of the treatment-effects of our diabetes medicines on these co-morbidities across broad patient populations that represent today's clinical practice in order to help more patients achieve treatment goals earlier in their disease.

Our industry-leading DapaCare clinical trial programme will enroll nearly 30,000 patients in RCTs and mechanistic studies exploring new ways to extend the therapeutic value of *Farxiga* to patients with and without type-2 diabetes, many of whom have not seen treatment advances in decades. DapaCare is our answer to the need for comprehensive research and treatment at a time when there is a fundamental shift in how diabetes, CV and renal diseases are managed.

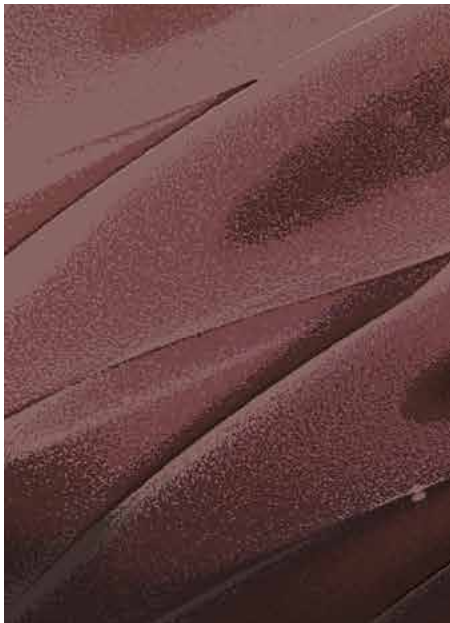
In addition to our leading CVOT, DECLARE (see case study on page 59), and our RWE study, CVD-REAL, we have invested in two pivotal *Farxiga* outcomes trials in HF, evaluating patients with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF), both in patients with and without type-2 diabetes. These, along with several mechanistic studies, make *Farxiga* a potential first-in-class treatment to address a significant unmet need in HF. Further research from the DapaCare programme is investigating renal outcomes and CV mortality in patients with CKD, the natriuretic effect and volume changes in type-2 diabetes with preserved or impaired renal function, and changes in proteinuria in non-diabetes and kidney diseases.

In type-1 diabetes, final results from the DEPICT programme trials were presented and published in 2018, and formed our regulatory submissions currently under review in the EU (EMA), Japan (PMDA) and the US (FDA), for *Farxiga* as an adjunct treatment to insulin for adults with type-1 diabetes. If approved, *Farxiga* may be the first selective SGLT-2 inhibitor with this indication, representing an important advancement for people with type-1 diabetes who have not seen meaningful treatment progression in decades. In February 2019, the Committee for Medicinal Products for Human Use (CHMP) of the EMA issued a positive recommendation from the EMA to use *Farxiga* in adults with type-1 diabetes as an adjunct to insulin in patients with BMI ≥ 27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy. Regulatory decisions for the type-1 indication are expected in the first half of 2019 in the EU and Japan. The US regulatory decision is expected in the second half of 2019.

Bydureon, our glucagon-like peptide-1 (GLP-1) receptor agonist for type-2 diabetes, has become more convenient and available this year to patients in multiple countries whose blood sugar remains uncontrolled with other treatments, supported by our Phase III trial, EXSCEL, the largest and longest CVOT on the GLP-1 class. Additionally, *Bydureon BCise*, a new formulation in an easy-to-use, once-weekly device that does not require titration, was approved by the EC. With 3Sbio Inc., we also gained approval for *Bydureon* across China, making it the first once-weekly GLP-1 in a nation with an estimated 114 million patients living with diabetes.

We are also advancing promising investigational agents that bring new approaches to metabolic diseases and their complications. In June, the first clinical results from a Phase IIa study conducted on MEDI0382, our oxyntomodulin-like peptide molecule being studied for patients with type-2 diabetes, were presented at the American Diabetes Association and simultaneously published in *The Lancet*, demonstrating the potential to become a first-in-class treatment for type-2 diabetes, NASH and obesity.

We follow the science to new clinical solutions for metabolic diseases and are working with leaders in the global diabetes community to overcome obstacles to optimal care. Led by Primary Care Diabetes Europe, we have partnered to launch Early Action in Primary Care to address clinical inertia and resistance to early use of innovative treatments like SGLT-2s and GLP-1s. In addition, with the research group, Health Economics and Outcomes Research, we will issue a first-of-its-kind predictive analysis on the economic value to health systems across Europe and the US of treating diabetes and CV complications together, with the goal of improving reimbursement policy and patient outcomes.



Science *can* advance our understanding of the repair and regeneration of tissues

For the estimated 26 million people worldwide with heart failure, recent scientific progress in blood vessel and heart muscle regeneration may lead to new ways of treating their disease. Not so long ago, we assumed that heart failure was an almost inevitable consequence of damage to or death of cells in the heart's main pumping chamber, the left ventricle, caused by lack of oxygen due to an impaired blood supply. However, we now know that there may be ways to help regeneration of blood vessels around heart muscle cells that are damaged by a heart attack, by high blood pressure or other cardiovascular problems that occur as people get older.

Our pioneering research is based on:

> Advances in understanding of vascular biology and the biological action of vascular endothelial growth factor A (VEGF-A) in stimulating formation of new blood vessels and helping to repair damaged heart muscle.
> Developments in messenger ribonucleic acid (mRNA) technology to boost production of VEGF-A in areas of the heart (mRNA is an essential part of the process by which genes in the form of DNA are decoded to make proteins).

The vascular and cardiac regeneration initiative brings together the complementary skills and expertise of scientists from AstraZeneca and Moderna. This important collaboration, which began in 2013, is advancing the science of tissue regeneration for cardiovascular and metabolic diseases and in other therapy areas. It is rapidly translating laboratory findings into clinical trials of novel therapeutic modalities, for example patients undergoing coronary artery bypass graft surgery (AZD8601).

26m

26 million people worldwide with heart failure

Stem cell differentiating into heart muscle (cardiac regeneration).

Respiratory

We aim to transform the treatment of asthma and COPD with our growing portfolio of inhaled and biologic medicines. Our research focuses on the underlying causes of respiratory diseases, using new modalities to pursue previously hard-to-reach targets, with the ambition of achieving remission or even cures for patients.

Unmet medical need and world market

Today, more than 700 million people have asthma or chronic obstructive pulmonary disease (COPD). About 250 million of these people are in our 12 largest commercial markets, but more than 175 million of these individuals do not receive maintenance treatment for these chronic diseases. Despite currently available medicines, therapeutic advances are needed to reduce morbidity and mortality.

We estimate that new medicines and Emerging Markets will drive 7% annual growth over the next decade, reaching $47 billion by 2028.

Cilia wafting in the lung with a small molecule overlay.

339m

Some 339 million individuals worldwide have asthma, with prevalence expected to rise. Severe asthma accounts for about 10% of asthma patients but 50% of the physical and socio-economic burden of asthma. Millions of patients underuse their anti-inflammatory maintenance controller treatments (which treat the underlying inflammation of the disease) and are reliant on reliever medications.

384m

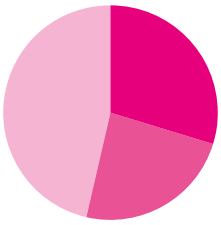
Globally, some 384 million people have COPD, and it is predicted to be the third leading cause of death by 2020. COPD exacerbations represent a significant burden for patients, carers and society. Even one severe exacerbation can significantly reduce lung function and is associated with higher mortality.

Therapy area world market

(MAT/Q3/18)

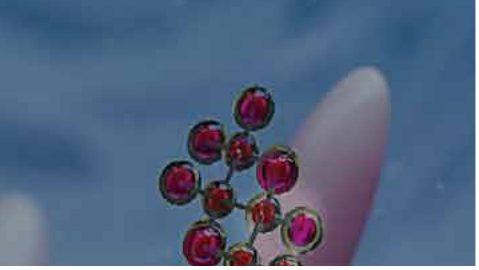
$68.4bn

Annual worldwide market value



- Asthma $20.5bn
- COPD $16.2bn
- Other $31.7bn

Source: IQVIA.
AstraZeneca focuses on specific segments within this overall therapy area market.



Key marketed products and revenues 2018

Our Respiratory business returned to growth in 2018, with sales of $4,911 million, up 4% (3% at CER). *Symbicort* held its position as the leading inhaled corticosteroid (ICS)/long-acting beta2-agonist (LABA) in volume sales. *Pulmicort* continued to deliver strong revenue growth, led by Emerging Markets in which China stood out. In biologics, *Fasenra* had strong launches in 35 markets and achieved leadership in new prescriptions in the IL-5 severe asthma class in the US and Japan.

Respiratory revenue

$4,911m

23% of total

2017: $4,706m

2016: $4,753m

Product	Disease area	Revenue	Commentary
Symbicort (budesonide/formoterol)	Asthma COPD	↓ $2,561m, down 9% (10% at CER)	Continued leadership of ICS/LABA class with revenue impacted by expected pricing pressure; AstraZeneca's largest medicine by sales.
Pulmicort (budesonide)	Asthma	↑ $1,286m, up 9% (8% at CER)	Brand growth led by Emerging Markets with leadership in China.
Fasenra (benralizumab)	Severe asthma	n/m $297m, movement n/m	Successful first year launch; leading the IL-5 class in new prescriptions (US and Japan).
Daliresp/Daxas (roflumilast)	COPD	↓ $189m, down 5% (5% at CER)	250mcg tablet approved as a starting dose in the US and Europe.
Tudorza/Eklira (aclidinium)	COPD	↓ $110m, down 27% (29% at CER)	Reflects the flat long-acting muscarinic antagonist (LAMA) market. Sales in the US declined by 62% reflecting the impact of federal purchases.
Duaklir (aclidinium/formoterol)	COPD	↑ $95m, up 20% (14% at CER)	Growth in Europe is in line with expectations.
Bevespi Aerosphere (glycopyrrolate/formoterol)	COPD	↑ $33m, up 106% (106% at CER)	*Bevespi Aerosphere* revenue and growth is in line with expectations based on focused investment in 2018, reflecting low class growth.
Others	Asthma COPD	↑ $340m, up 20% (18% at CER)	Mature portfolio. Divestment of rights to *Alvesco*, *Omnaris* and Zetonna to Covis.

Our strategy for Respiratory

Respiratory is one of our main therapy areas, and our medicines reached more than 18 million patients as maintenance therapy in 2018. We have a strong pipeline with more than 33,000 patients participating in Phase I-IV respiratory clinical trials across the world.

Our ambition is to transform outcomes for patients with respiratory diseases through:

1. Our strength in inhaled combination medicines.
2. A leading biologics portfolio.
3. A robust early pipeline where our goal is to achieve disease modification, early intervention and cure.

In inhaled medicine, our focus is on two key areas of clinical care. In asthma, we are working to prevent attacks by reducing over-reliance on reliever monotherapy and advancing anti-inflammatory reliever therapy, which is now under regulatory review for a licence extension based on the landmark *Symbicort Turbuhaler* SYGMA trials. We continue to invest in *Symbicort* given its value in the treatment of asthma and COPD, also reflected by its continued leadership in the ICS/LABA class. In COPD, we are advancing our next generation inhaled *Aerosphere* portfolio with the ambition of reducing exacerbation rates using our investigational triple therapy, PT010, earlier in the course of the disease than recommended in guidelines today.

In biologics, we aim to transform outcomes among patients with the greatest unmet medical need and relegate chronic oral steroid use to last resort, given its association with adverse events. Our first respiratory biologic, *Fasenra*, is for severe eosinophilic asthma and is being investigated for other eosinophil-driven diseases. Approved in November 2017, *Fasenra* already leads the IL-5 class in new prescriptions in the US and Japan. In the future, tezepelumab, a potential first-in-class anti-thymic stromal lymphopoietin (TSLP) mAb that blocks a key upstream driver of inflammation in asthma, has the potential to become "the broadest biologic for the treatment of persistent uncontrolled asthma seen to date"* if the Phase III programme reflects the positive Phase IIb data, as noted in the *New England Journal of Medicine*.

Our early pipeline continues to grow and includes new drug modalities allowing us to address hard-to-reach targets in the lung that were previously seen as inaccessible, for example: the *Anticalin* protein AZD1402, an inhaled IL4Rα antagonist currently in Phase I development for asthma, in collaboration with Pieris Pharmaceuticals.

Our respiratory market leadership in China positions us well to support improvements in acute treatment using our leading nebulisation portfolio and establishing maintenance inhaled treatment as the standard of care in asthma and COPD. Each day the paediatric nebulisation programme we support treats 300,000 patients, enabling them to receive guideline-recommended acute care for their condition.

* Elisabeth H. Bel. Moving Upstream – Anti-TSLP in Persistent Uncontrolled Asthma. *New England Journal of Medicine*. 2017; 377:10.

2018 pipeline highlights

The progress of our pipeline in 2018 reflects our commitment to transforming critical areas of care in respiratory.

We advanced *Symbicort Turbuhaler* and PT027 (ICS/SABA combination) as anti-inflammatory reliever therapies in asthma. With PT010, our inhaled triple therapy, we made our first regulatory submissions and published positive Phase III KRONOS data that demonstrated its potential to improve lung function in patients with COPD. KRONOS data also demonstrated the potential to significantly reduce exacerbation risk versus LAMA/LABA in a patient population that was not required to have had an exacerbation in the previous 12 months (a population classified as GOLD B in international guidelines, where triple therapy is currently not recommended). In line with our strategy to transform outcomes with respiratory biologics, *Fasenra* was granted additional regulatory approvals around the world for severe, eosinophilic asthma, while our anti-TSLP biologic, tezepelumab, was granted US FDA Breakthrough Therapy designation (our first for a respiratory medicine) for severe asthma patients without an eosinophilic phenotype, including those who are ineligible for biologic therapies today.

Full details of our pipeline are given in the Development Pipeline from page 212 and highlights from the progress our Respiratory pipeline made against our KPIs in 2018 are shown below.

Life-cycle phases – R&D

New molecular entity (NME) Phase II starts/progressions

Product	Disease
None	–

NME and major life-cycle management (LCM) positive Phase III investment decisions

Our co-development partner, Avillion, achieved first subjects in the PT027 Phase III programme. PT027 is an investigational fixed-dose combination of budesonide (an inhaled corticosteroid) and albuterol (a short-acting beta2-agonist).

Product	Disease
PT027*	Asthma

Plus one project where investment decision has been made.

* Led by partner Avillion.

NME and major LCM regional submissions

Key regulatory acceptances included our first filings for PT010 (triple therapy) in COPD in Japan and China, and *Symbicort* as an anti-inflammatory reliever in mild asthma in the EU.

Product	Disease	Region
Bevespi Aerosphere	COPD	Japan, China
Fasenra	Self administration, autoinjector (GRECO/GREGALE)	EU, US
PT010	COPD	Japan, China
Symbicort	Mild asthma	EU

Life-cycle phases – approvals

NME and major LCM regional approvals

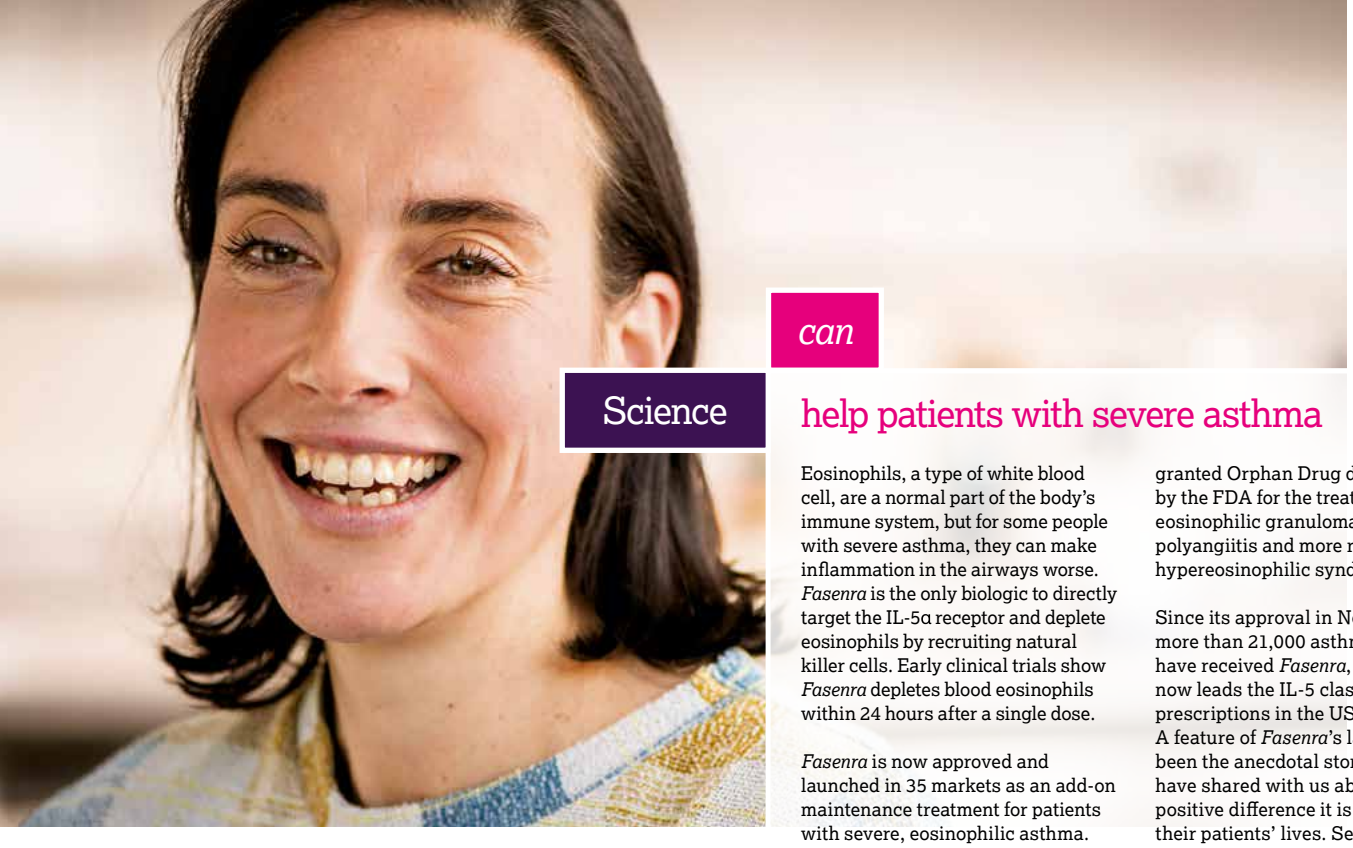
Further regional approvals were seen with *Fasenra* for severe asthma in Japan and severe eosinophilic asthma in the EU – with the product now launched in more than 35 markets and *Bevespi Aerosphere* for COPD in the EU.

Product	Disease	Region
Bevespi	COPD	EU
Fasenra	Severe asthma	EU, Japan

Discontinued projects

Product	Disease	Reason
AZD7594 + abediterol	COPD	Safety/efficacy

For more information on the life-cycle of a medicine, see page 9.



Science *can* help patients with severe asthma

Eosinophils, a type of white blood cell, are a normal part of the body's immune system, but for some people with severe asthma, they can make inflammation in the airways worse. *Fasenra* is the only biologic to directly target the IL-5α receptor and deplete eosinophils by recruiting natural killer cells. Early clinical trials show *Fasenra* depletes blood eosinophils within 24 hours after a single dose.

Fasenra is now approved and launched in 35 markets as an add-on maintenance treatment for patients with severe, eosinophilic asthma. Patients receive *Fasenra* as a fixed-dose subcutaneous injection via a pre-filled syringe every eight weeks after initial loading doses. *Fasenra* has been investigated for self-administration and in an autoinjector device; regulatory submissions were made in 2018 and we anticipate decisions in 2019. In addition, *Fasenra* is being investigated for indications in other eosinophil-driven diseases, including severe nasal polyposis, and has been granted Orphan Drug designation by the FDA for the treatment of eosinophilic granulomatosis with polyangiitis and more recently, hypereosinophilic syndrome.

Since its approval in November 2017, more than 21,000 asthma patients have received *Fasenra*, which now leads the IL-5 class in new prescriptions in the US and Japan. A feature of *Fasenra*'s launch has been the anecdotal stories clinicians have shared with us about the positive difference it is having on their patients' lives. Severe asthma is a debilitating disease, which impacts many aspects of a patient's life and these stories reflect the difference an effective biologic medicine can have for these patients.

The launch success of *Fasenra* also supports our view that biologic treatment rates will significantly increase in the coming years in line with the evolution of treatment in other inflammatory diseases.

2018 review – strategy in action

Strength in inhaled combination medicines

Our strength in inhaled combination medicines was reflected in 2018 with *Symbicort*, which retained its position as the number one ICS/LABA combination globally in volume terms and is a cornerstone of current asthma and COPD care. We continue to invest in *Symbicort*, which remains AstraZeneca's number one medicine in Product Sales in 2018.

Pricing pressure continues to impact *Symbicort* performance but was in line with expectations as prices rebase ahead of anticipated generic entries. This trend continues to be offset by Emerging Market growth, led by demand for acute and maintenance care in China. In March, the NMPA approved *Symbicort Turbuhaler* as a maintenance and reliever therapy, designed for the treatment of asthma in adolescent patients (12-17 years) in China.

In May 2018, positive results from the Phase III SYGMA trials of *Symbicort Turbuhaler* were published in the *New England Journal of Medicine* and presented at the American Thoracic Society International Congress. The trials, which met their primary objectives, evaluated the efficacy of *Symbicort Turbuhaler*, taken only as needed without maintenance therapy, as an anti-inflammatory reliever compared with standard of care medicines for mild asthma. In November, we announced that the Swedish Medical Products Agency had accepted our regulatory submission for the EU to expand the indication for *Symbicort Turbuhaler*, as an anti-inflammatory reliever as needed, in patients with mild asthma. Millions of patients with asthma are reliant on their reliever medications, which improve symptoms but do not treat the inflammation of this disease, and they underuse anti-inflammatory maintenance controller treatments, resulting in preventable exacerbations. In China, the Chinese Journal of General Practitioners guidelines were updated to incorporate the SYGMA data. This update recommended *Symbicort* as a potential treatment for all asthma severities.

We significantly progressed all Phase III trials supporting PT010 – KRONOS, SOPHOS, TELOS and ETHOS. The Phase III KRONOS trial was published in September in *The Lancet Respiratory Medicine*. KRONOS evaluated the efficacy and safety of triple combination therapy, PT010, versus dual combination therapies *Bevespi Aerosphere*, *Symbicort Turbuhaler* and PT009. In the trial, PT010 met six of seven primary endpoints versus dual comparators and PT009 met two non-inferiority endpoints to support the qualification of PT009 as an active comparator. In a key secondary endpoint, PT010 showed a statistically significant 52% reduction in the rate of moderate or severe COPD exacerbations compared with *Bevespi Aerosphere* in a patient population that was not required to have had an exacerbation in the previous 12 months. The adverse events profile was consistent with that observed in previous trials and the incidence of adjudicated pneumonia was low and comparable in all treatment arms.

During the first half of 2018, the Phase III SOPHOS trial read out, which compared two doses of PT009 to PT005. PT009 met its primary endpoint and delivered superior efficacy to PT005 at morning pre-dose through forced expiratory volume (FEV) 1 at Week 24. In September 2018, the TELOS Phase III trial, which investigated the efficacy and safety of PT009 in patients with moderate to very severe COPD, regardless of whether or not they had had an exacerbation in the prior year, showed that PT009 is an effective maintenance treatment for patients with COPD and a suitable comparator for PT010. The data were presented at the European Respiratory Society Congress and were published in the *European Respiratory Journal*. SOPHOS and TELOS were designed to qualify PT009 as an active comparator in the PT010 clinical trial programme.

In July 2018, the ETHOS Phase III trial, which further investigates the efficacy and safety of PT010, completed enrolment of 8,400 patients across 28 countries.

In addition, during the second half of 2018, the regulatory submissions for PT010 were accepted by the Japan MHLW and the China NMPA, based on the KRONOS Phase III trial. In January 2019, PT010 received Priority Review designation from China's NMPA.

Bevespi Aerosphere's progress also continued in 2018 with regulatory approvals in Canada and Australia. In December 2018, the European Commission approved *Bevespi Aerosphere* in a pressurised metered-dose inhaler (pMDI) as a maintenance dual bronchodilator treatment to relieve symptoms in adult patients with COPD. In Japan and China, the regulatory submissions for *Bevespi Aerosphere* were accepted during the third quarter of the year.

In August 2018, we announced top-line results from the AERISTO Phase IIIb trial for *Bevespi Aerosphere* in patients with moderate to very severe COPD. In the trial, *Bevespi Aerosphere* demonstrated non-inferiority to umeclidinium/vilanterol on peak FEV1 but did not demonstrate superiority on peak FEV1 or non-inferiority on trough FEV1. The efficacy and safety of *Bevespi Aerosphere* has been established by the Phase III PINNACLE trial programme involving more than 5,000 patients.

Our medicines partnered with Circassia also made progress. In the second half of 2018, the FDA accepted the *Duaklir* NDA for the maintenance treatment of patients with COPD. We anticipate a Prescription Drug User Fee Act action date in the first half of 2019. In the first half of 2018, on behalf of Circassia, we submitted an sNDA for *Tudorza* to the FDA. The submission was based on the results from the ASCENT trial, which achieved its co-primary endpoints for safety (no increase in cardiovascular risk MACE) and efficacy (COPD exacerbation reduction). It is anticipated that the US label will be updated accordingly in the first half of 2019. In December 2018, Circassia announced plans to acquire the full rights to *Tudorza* in the US.

In addition, a 250mcg tablet for *Daliresp/Daxas* was approved by the FDA in January 2018 and the EMA in April 2018 to be used as a starting-dose treatment for the first four weeks, followed by an increase to the maintenance dosage of 500mcg. *Daxas* is indicated for maintenance treatment of severe COPD associated with chronic bronchitis in adult patients with a history of frequent exacerbations, as an add-on to bronchodilator treatment.

In May 2018, Phase IIa data for AZD8871 were presented in a late-breaking oral presentation at the American Thoracic Society International Congress 2018. AZD8871 is an inhaled long-acting dual muscarinic antagonist/β2 adrenoceptor agonist under development for the treatment of COPD.

Biologic medicines

Our first respiratory biologic, *Fasenra*, continued to receive product approvals in 2018 with launches in more than 35 countries. In January 2018, the EMA approved *Fasenra* as an add-on maintenance treatment in adult patients with severe, inadequately controlled eosinophilic asthma, despite their treatment with high-dose ICS plus LABA. In Japan, *Fasenra* was approved as an add-on treatment for bronchial asthma in patients who continue to experience asthma exacerbations despite treatment with high-dose ICS and other asthma controller(s).

Currently only 10% of eligible patients in our top 12 commercial markets receive a biologic treatment, whereas biologic treatment rates in more mature inflammatory disease markets, such as rheumatoid arthritis and psoriasis, are 30–50% and growing. The main factors that will drive the rate of growth include: availability of effective medicines; improved clinical capabilities and capacity for severe asthma; and administration of biologics and evidence enabling the reduction or discontinuation of maintenance oral corticosteroid use. AstraZeneca is investing to accelerate these drivers 'beyond the medicine' which should support biologics having the kind of impact that they have had in other inflammatory diseases. The opportunity to transform more lives is significant.

In May 2018, we announced top-line results from two Phase III trials, GALATHEA and TERRANOVA, for *Fasenra* in patients with moderate to very severe COPD. The trials did not meet their primary endpoints of a statistically significant reduction of exacerbations. We are reviewing the full data set and do not currently intend to make a regulatory submission in COPD based on these data.

In September 2018, results from the BORA Phase III extension trial evaluating the long-term safety and efficacy of *Fasenra* as an add-on maintenance treatment in patients with severe eosinophilic asthma who had previously completed one of the two pivotal placebo-controlled SIROCCO or CALIMA Phase III trials, were presented in a late-breaking oral presentation at the European Respiratory Society International Congress 2018, and subsequently published in *The Lancet Respiratory Medicine* in November. In BORA, *Fasenra* showed a safety and tolerability profile similar to that observed in the predecessor trials, with no increase in the frequencies of overall or serious adverse events.

Improvements in efficacy measures observed with *Fasenra* in SIROCCO or CALIMA were maintained over the second year of treatment. During the first quarter of 2018, we also commenced a Phase III trial of *Fasenra* for the treatment of nasal polyposis. During the second quarter, we commenced the Phase IIIb PONENTE trial further evaluating *Fasenra*'s potential to eliminate maintenance oral corticosteroid use in patients with severe refractory eosinophilic asthma.

During the third quarter of 2018, the SOLANA Phase IIIb trial did not meet its primary endpoint. SOLANA is a randomised, double-blinded, parallel group, placebo-controlled Phase IIIb trial. The trial is designed to evaluate the onset and maintenance of effect and the safety of *Fasenra* in patients with severe, eosinophilic asthma. We are evaluating the full data set and anticipate the results will be submitted for publication in a medical journal.

In November 2018, the FDA granted Orphan Drug designation for *Fasenra* for the treatment of eosinophilic granulomatosis with polyangiitis. In February 2019, *Fasenra* was also granted Orphan Drug designation for the treatment of hypereosinophilic syndrome.

In the fourth quarter of 2018, we submitted regulatory filings in the US and the EU for the addition of self-administration and an autoinjector device for *Fasenra* in severe asthma. Decisions are anticipated in 2019.

In September 2018, with our partner Amgen, we announced that the FDA had granted Breakthrough Therapy designation for tezepelumab in patients with severe asthma without an eosinophilic phenotype, including those who are ineligible for biologic therapies today. This was the seventh Breakthrough Therapy designation we have received from the FDA since 2014, and the first in respiratory medicine. Tezepelumab is currently in development in the Phase III PATHFINDER clinical trial programme.

Other Disease Areas

We have medicines and vaccines in other disease areas that have an important impact for patients. As such, we are selectively active in the areas of autoimmunity, infection, neuroscience and gastroenterology, where we follow an opportunity-driven approach and often work through partnerships.

Unmet medical need and world market

The WHO estimates that seasonal influenza may result in 290,000 to 650,000 deaths each year due to respiratory diseases alone.

Key marketed products and revenues 2018

Nexium is continuing to perform strongly in China, while sales for the rest of the world are in line with expectations given pressures from generic competition. Following the renewed recommendation from the Advisory Committee on Immunization Practices of *FluMist* Quadrivalent in the US, *FluMist* returned to the US market in the third quarter.

Revenue from other products

$3,400m

16% of total

2017: $4,156m

2016: $5,067m

Product	Disease area	Revenue	Commentary
Infection			
Fluenz Tetra/ *FluMist* Quadrivalent (live attenuated influenza vaccine)	Influenza	↑ $110m, up 41% (44% at CER)	Approved in the US, EU, Canada, Israel and Hong Kong. *FluMist* returned to the US market in the third quarter of 2018, in time for the 2018-2019 influenza season. Daiichi Sankyo holds rights to *Fluenz* Tetra/ *FluMist* Quadrivalent in Japan.
Synagis (palivizumab)	Respiratory syncytial virus (RSV)	↓ $665m, down 3% (3% at CER)	Divested US rights to Sobi. AbbVie holds rights to *Synagis* outside the US.
Neuroscience			
Movantik/ *Moventig* (naloxegol)	Opioid induced constipation	↓ $109m, down 11% (11% at CER)	Licensed from Nektar Therapeutics. Kyowa Hakko Kirin has held rights in the EU since March 2016. Knight Therapeutics Inc. has held rights in Canada and Israel since December 2016. Co-commercialisation in the US with Daiichi Sankyo.
Seroquel IR/ *Seroquel XR* (quetiapine fumarate)	Schizophrenia Bipolar disease	↓ $361m, down 29% (31% at CER)	Luye Pharma holds rights to *Seroquel* and *Seroquel XR* in the UK, China and other international markets. The rights to *Seroquel* and *Seroquel XR* in Japan are partnered with Astellas.
Vimovo (naproxen and esomeprazole)	Osteoarthritic pain	↓ $70m, down 11% (13% at CER)	Licensed from Pozen and divested worldwide rights (ex-US) to Grünenthal in October 2018. Divested US rights to Horizon Pharma Inc. since November 2013.
Gastroenterology			
Losec/ *Prilosec* (omeprazole)	Proton pump inhibitor to treat acid-related diseases	↔ $272m, flat (down 2% at CER)	
Nexium (esomeprazole)	Proton pump inhibitor to treat acid-related diseases	↓ $1,702m, down 13% (14% at CER)	Divested European rights to Grünenthal in October 2018.

Therapy Area Review
Other Disease Areas
continued

Our strategy for Other Disease Areas and 2018 pipeline highlights

Our approach in these other disease areas looks to maximise revenue through externalisation and on-market products, advance the novel product pipeline with partnerships where appropriate, and preserve a stake in the most promising assets.

Full details of our pipeline are given in the Development Pipeline from page 212 and highlights from the progress of our Other Disease Areas pipeline made in 2018 against our KPIs are shown below.

Life-cycle phases – R&D

New molecular entity (NME) Phase II starts/progressions

Product	Disease
AZD9567	Rheumatoid arthritis
MEDI7352	Painful diabetic neuropathy

NME and major life-cycle management (LCM) positive Phase III investment decisions

Product	Disease
None	–

NME and major LCM regional submissions

Product	Disease	Region
None	–	–

Life-cycle phases – approvals

NME and major LCM regional approvals

An additional regional approval was seen with *Nexium* in Japan, which enables and increases patient access to this medicine.

Product	Disease	Region
*Linzess**	Irritable bowel syndrome with constipation	China
Nexium	Paediatric and sachet gastroesophageal disease (GERD)	Japan

* Approved in January 2019.

Discontinued projects

Product	Disease	Reason
Lanabecestat	BACE early Alzheimer's disease	Safety/efficacy
MEDI9314	IL4R atopic dermatitis	Strategic

For more information on the life-cycle of a medicine, see page 9.

2018 review – strategy in action

Infection

Seasonal influenza is a serious public health problem that causes severe illness and death in high-risk populations. In 2018, the US Advisory Committee on Immunization Practices, under the Centers for Disease Control and Prevention, reinstated its recommendation that *FluMist* Quadrivalent (live attenuated influenza vaccine – LAIV) should be used in the US for the 2018-2019 influenza season. The recommendation followed a presentation of positive results from a US study in children between the ages of 2 to <4 years evaluating the shedding and antibody responses of the H1N1 strain in *FluMist* Quadrivalent. The study demonstrated that the new 2017-2018 H1N1 LAIV post-pandemic strain (A/Slovenia) performed significantly better than the 2015-2016 H1N1 LAIV post-pandemic strain (A/Bolivia), which was previously associated with reduced effectiveness. The antibody response induced with the new H1N1 LAIV strain was comparable to earlier data seen with the highly effective H1N1 LAIV strain included in the vaccine before the 2009 influenza pandemic.

In 2018, Public Health England released provisional vaccine effectiveness (VE) data from the recent 2017-2018 influenza season. VE across all vaccine types was low against the circulating A/H3N2 virus, and all influenza manufacturers are continuing to work with public health authorities to optimise protection against influenza. These latest data also demonstrated *Fluenz* Tetra provided good protection against H1N1 post-pandemic and influenza B strains during the 2017-2018 season, further supporting the improvements made in characterising and selecting H1N1 post-pandemic LAIV strains following our recent investigation into reduced effectiveness.

FluMist Quadrivalent/*Fluenz* Tetra continues to be licensed in multiple markets, including the US, Canada, EU, Israel and Hong Kong, and it remains a central part of the UK and Finnish paediatric national influenza vaccination programmes. We also have an ongoing agreement with the WHO to donate and supply stock at reduced prices in the event of an influenza pandemic.

MEDI8852, an investigational human mAb for the treatment of patients hospitalised with Type A strain influenza, obtained a grant from the US Department of Defense to conduct a Phase I/IIa study in September 2018. It received Fast Track designation from the FDA in March 2016.

Respiratory syncytial virus (RSV) is a common seasonal virus and the most prevalent cause of lower respiratory tract infections (LRTI) among infants and young children. It is the leading cause of hospitalisations and admissions to paediatric intensive care units and leads to nearly 150,000 deaths globally in children under five years of age, with the majority of deaths occurring in developing countries. Since its initial approval in 1998,

Synagis has become the global standard of care for RSV prevention and helps protect at risk babies against RSV. *Synagis* is approved in more than 80 countries and we continue to work with our worldwide partner, AbbVie, outside the US, to protect vulnerable infants.

In November 2018, we announced the divestment of *Synagis*' US rights to Sobi. Sobi will commercialise *Synagis* in the US and around 130 AstraZeneca employees will transfer to Sobi as part of the transaction. Sobi also has the right to participate in payments from the US profits and losses for MEDI8897.

MEDI8897, an extended half-life RSV mAb being investigated for the prevention of LRTI caused by RSV in infants and young children, is progressing in collaboration with Sanofi. It is being developed for use among a broad population of late pre-term and healthy full-term infants, so that they may only require one dose during an RSV season. In November 2018, we announced that the primary analysis for the pivotal, Phase IIb trial to evaluate the safety and efficacy of MEDI8897 showed that the trial met its primary endpoint. Following these results, in January 2019, the EMA granted MEDI8897 access to its PRIME (PRIority MEdicines) scheme and in February 2019, the FDA granted Breakthrough Therapy designation for MEDI8897.

Neuroscience

In June 2018, we announced with Lilly, the discontinuation of the Phase III clinical trials of lanabecestat, an oral beta secretase cleaving enzyme (BACE) inhibitor, for the treatment of Alzheimer's disease. The decision was based on recommendations by an independent data monitoring committee, which concluded that both the AMARANTH trial, in early Alzheimer's disease, and the DAYBREAK-ALZ trial, in mild Alzheimer's disease dementia, were not likely to meet their primary endpoints upon completion and therefore should be stopped for futility. As a result of this decision, the related AMARANTH extension trial was also discontinued. High-level results in December 2018 of the AMARANTH and DAYBREAK-ALZ trials confirmed no significant disease slowing was observed in any of the Phase III trials, confirming that the action to discontinue the trials was the correct decision.

We also collaborate with Lilly on MEDI1814, an antibody selective for amyloid-beta 1-42 (Aβ1-42) that is currently in Phase I trials as a potential disease-modifying treatment for Alzheimer's disease.

We are progressing MEDI7352 in painful diabetic neuropathy, which is in Phase II and continue our collaboration with Takeda on MEDI1341 for Parkinson's disease, which is in Phase I.

In May 2018, we announced an agreement with Luye Pharma for the sale and licence of the rights in the UK, China and other international markets to *Seroquel* and *Seroquel XR*. We had previously partnered the rights to *Seroquel* and *Seroquel XR* in Japan and Venezuela under prior agreements. *Seroquel*, used primarily to treat schizophrenia and bipolar disease, has lost its compound patent protection globally. The *Seroquel XR* formulation patents have now also expired in the majority of markets.

Autoimmunity and inflammation

In February 2018, six molecules from our early-stage inflammation and autoimmunity programmes were spun out into an independent biotech company, Viela Bio. The new company will focus on developing medicines for severe autoimmune diseases by targeting the underlying causes of each disease. The molecules include inebilizumab, currently in Phase II trial development for the treatment of neuromyelitis optica spectrum disorder, a rare condition that affects the optic nerve and spinal cord in approximately five in 100,000 people.

We announced in August 2018 that anifrolumab, a developmental mAb that inhibits the activity of all type I interferons (IFN), did not meet the primary endpoint in the TULIP 1 Phase III trial in systemic lupus erythematosus (SLE). A full evaluation of the combined TULIP 1 and TULIP 2 data will be conducted to determine next steps for anifrolumab in SLE. The Phase II trials in lupus nephritis and for a subcutaneous route of administration in SLE remain ongoing, as does the long-term extension trial in SLE.

In April 2016, AstraZeneca licensed its US rights to develop and commercialise *Zurampic* and *Duzallo* to Ironwood. In August 2018, Ironwood notified AstraZeneca of its intent to terminate the licence for convenience. In November 2018, Ironwood notified the FDA that it had discontinued the manufacturing of the products and contemporaneously informed AstraZeneca that it is working on withdrawing the NDAs for these products and terminating the FDA required post-marketing study. This process is expected to take several months.

Gastrointestinal

Use of *Nexium* continued to grow in a limited number of markets such as China and Japan in 2018. This growth is expected to continue following additional approvals in China for high-dose treatment of peptic ulcer bleeding and in Japan for paediatric patients from the age of one, with the innovative *Nexium* sachet formulation. The re-examination periods for adult indications/dosage of *Nexium* capsules and *Nexium* sachets have been extended for two years in Japan, until 30 June 2021. This enables the completion of another clinical trial for long-term treatment in the new paediatric population. *Nexium* is subject to generic competition globally, except for Japan.

In October 2018, we announced that we had entered into an agreement with Grünenthal for the rights to *Nexium* in Europe and *Vimovo* worldwide (excluding the US).

In January 2019, Ironwood announced they had received marketing authorisation from the NMPA in China for *Linzess* for the treatment of patients with irritable bowel syndrome with constipation. We entered into a collaboration in China with Ironwood in 2012.

Our products

While this Therapy Area Review concentrates on our key marketed products, many of our other products are crucial to our business in certain countries in Emerging Markets.

For more information on our potential new products and product life-cycle developments, please see the Therapy Area pipeline tables on pages 52, 58, 64 and 68 and the Development Pipeline table from page 212. For information on Patent Expiries of our Key Marketed Products, see from page 217.

Indications for each product described in this Therapy Area Review may vary among countries. Please see local prescribing information for country-specific indications for any particular product.

For those of our products subject to litigation, information about material legal proceedings can be found in Note 29 to the Financial Statements from page 194.

Details of relevant risks are set out in Risk from page 220.

Risk Overview

We face a diverse range of risks and uncertainties. Those risks which have the potential to have a material impact on our business or results of operations are our Principal Risks.

The Board has carried out a robust assessment of the Principal Risks facing the Group, including those that threaten its business model, future performance, solvency or liquidity. The table overleaf provides insight into the ongoing Principal Risks, outlining why effective management of these risks is important and relevant to the business, how we are managing them and which risks are rising, falling or have remained static during the past 12 months.

Our approach to risk management is designed to encourage clear decision making on which risks we take and how we manage these risks. Fundamental to this process is a sound understanding of every risk's potential strategic, commercial, financial, compliance, legal and reputational implications.

Further information on our key risk management and assurance processes can be found in Risk from pages 220 to 230 which also includes a description of circumstances under which principal and other risks and uncertainties might arise in the course of our business and their potential impact.

Progress in the delivery of Group-wide restructuring initiatives has been sufficient for the Board to determine that the risk 'Delivery of Gains from Productivity Initiatives' (previously listed as a Principal Risk) is no longer a Principal Risk. The Board will, however, continue to monitor strategic initiatives and their impact on employee engagement.

Managing risk

We work to ensure that we have effective risk management processes in place to support the delivery of our strategic priorities. This enables us to meet the expectations of our stakeholders and upholds our Values. We monitor our business activities and external and internal environments for new, emerging and changing risks to ensure that these are managed appropriately. The Board believes that existing processes provide it with adequate information on the risks and uncertainties we face. Details of these risks and the potential impacts on our business are contained on pages 220 to 230.

Risk management embedded in business processes

We strive to embed sound risk management in our strategy, planning, budgeting and performance management processes.

The Board defines the Group's risk appetite, enabling the Group, in both quantitative and qualitative terms, to judge the level of risk it is prepared to take in achieving its overall objectives. The Board expresses the acceptable levels of risk for the Group using three key dimensions. These are: (i) earnings and cash flow; (ii) return on investment; and (iii) ethics and reputation. Annually, the Group develops a detailed three-year bottom-up business plan and 10-year long-range projection to support the delivery of its strategy. The Board considers these in the context of the Group's risk appetite. Adjustments are made to the plan or risk appetite to ensure they remain aligned. Our risk management approach is aligned to our strategy and business planning processes. We cross-check financial risks and opportunities identified through the business planning process and integrate our findings into the overall risk management reporting. Line managers are accountable for identifying and managing risks and for delivering business objectives in accordance with the Group's risk appetite.

The SET is required by the Board to oversee and monitor the effectiveness of the risk management processes implemented by management. Within each SET function, leadership teams discuss the risks the business faces. Every year, we map these risks to AstraZeneca's risk 'taxonomy'. This process provides a Group-wide assessment for the Board, Audit Committee and SET. Quarterly, each SET function assesses changes to these risks, new and emerging risks, and mitigation plans. These are assimilated into a Group Risk Report for the Board, Audit Committee and SET. Supporting tools are in place to assist risk leaders and managers in managing, monitoring and planning for risk, and we continue to work on developing our risk management standards and guidelines. Global Compliance, Finance and Internal Audit Services support SET by

advising on policy and standard setting, monitoring and auditing, and communication and training, as well as reporting on the adequacy of line management processes as they apply to risk management.

We have a business resilience framework which governs our ability to prevent or quickly adapt to situations while maintaining continuous business operations and safeguarding our people, processes and reputation. Within this we have business continuity plans to address situations in which specific risks have the potential to severely impact our business. These plans include training and crisis simulation activities for business managers.

More information about our Global Compliance function and the Code of Ethics can be found in the Corporate Governance Report from page 91.

Viability statement

In accordance with provision C.2.2 of the 2016 UK Corporate Governance Code, the Board has determined that a three-year period to 31 December 2021 constitutes an appropriate period over which to provide its viability statement.

The Board considers annually and on a rolling basis, a three-year bottom-up detailed business plan. The Board also assesses the Company's prospects using a 10-year long-range projection but, given the inherent uncertainty involved, believes that the three-year statement presents readers of this Annual Report with a reasonable degree of assurance while still providing a longer-term perspective.

The three-year detailed business plan captures risks to the sales and cost forecasts at a market and SET function level. The plan is used to perform central net debt and headroom profile analysis. The following scenarios have been applied to this analysis to create a severe downside reflecting some of the Principal Risks detailed on pages 72 to 73.

> **Scenario 1** Principal Risk: demand, pricing, market access and competitive pressures; quality and execution of commercial strategies; secure and protect product IP. Lower than anticipated growth rates, adverse impact of generic competition and greater than anticipated pressure on pricing across multiple products and markets.
> **Scenario 2** Principal Risk: delivery of pipeline and new products. Assumes no launches of new products.
> **Scenario 3** Principal Risk: maintain supply of compliant, quality product. Regulatory observation or other equipment failure results in a 12-month outage at one of our key manufacturing sites.
> **Scenario 4** Principal Risk: achieve strategic plans and meet targets and expectations. Income from divestment of core assets reinvested into core therapy areas and new products reduced by half.
> **Scenario 5** Principal Risk: externally driven demand, pricing, access and competitive pressures. Failure to establish EU-based regulatory testing and release capability for a product leads to inability to supply impacted products into the EU following a 'no deal Brexit' outcome.
> **Scenario 6** Principal Risk: meet regulatory and ethical expectations on commercial practices including bribery and corruption and scientific exchanges. Legal, regulatory non-compliance or cyber incident causes reputational damage in a key market resulting in a significant and ongoing reduction in market share.

In addition, the Board has considered more stressed scenarios including restrictions on debt factoring and no access to capital markets to raise new debt. In each scenario or combination of scenarios above, the Group is able to rely on its committed credit facilities, leverage its cost base, reduce capital expenditure and take other cash management measures to mitigate the impacts and still have residual capacity to absorb further shocks.

Based on the results of this analysis, the Directors have a reasonable expectation that the Company will be able to continue in operation and meet its liabilities as they fall due over the three-year period of their assessment.

Brexit

On 23 June 2016, the UK held a referendum on the UK's continuing membership of the EU, the outcome of which was a decision for the UK to leave the EU (Brexit). The progress of current negotiations between the UK Government and the EU and the ratification of the outcome of those negotiations by the UK and EU parliaments will likely determine the future terms of the UK's relationship with the EU, as well as to what extent the UK will be able to continue to benefit from the EU's single market and other arrangements. Until the Brexit negotiation and parliamentary ratification processes are completed, it is difficult to anticipate the potential impact on AstraZeneca's market share, sales, profitability and results of operations. The Group operates from a global footprint and retains flexibility to adapt to changing circumstances. The uncertainty during and after the period of negotiation is also expected to increase volatility and may have an economic impact, particularly in the UK and Eurozone. The Group has responded by engaging proactively with key external stakeholders and establishing a cross-functional internal steering and implementation committee to understand, assess, plan and implement operational actions that may be required. Many of these actions are being implemented based on assumptions rather than defined positions so that the Group is able to mitigate the risks arising from variable external outcomes. The Group has adopted a base case planning assumption of hard Brexit/No deal since the time of the referendum and has taken appropriate actions to date based on those assumptions. Currently, many actions have been implemented or are in process including, but not limited to: engagement with government and regulators; duplication of release testing and procedures for products for the EU27 and the UK markets; transfer of regulatory licences, re-design of packaging and labelling, additional inventory builds and changes to logistics plans and shipping routes; customs and duties set up for introduction or amendment of existing tariffs or processes; associated IT systems reconfigurations; and banking arrangement changes. The Board reviews the potential impact of Brexit regularly as an integral part of its Principal Risks (as outlined overleaf) rather than as a standalone risk. The Board most recently reviewed the Group's Brexit readiness plans at its meeting in December 2018 and continues to assess its impact.

Risk Overview
continued

Principal Risks

Strategy key

- Achieve Scientific Leadership
- Return to Growth
- Be a Great Place to Work
- Achieve Group Financial Targets

Trend key

- Increasing risk
- Decreasing risk
- Unchanged

Risk category and Principal Risks	Context/potential impact	Management actions	Trend versus prior year
Product pipeline and intellectual property			
Delivery of pipeline and new products	The development of any pharmaceutical product candidate is a complex, risky and lengthy process involving significant financial, R&D and other resources. A project may fail or be delayed at any stage of the process due to a number of factors, which could reduce our long-term growth, revenue and profit	> Prioritise and accelerate our pipeline > Strengthen pipeline through acquisitions, licensing and collaborations > Focus on innovative science in three main therapy areas	Unchanged
Meet quality, regulatory and ethical drug approval and disclosure requirements	Our pharmaceutical products and commercialisation processes are subject to extensive regulation. Delays in regulatory reviews and approvals impact patients and market access, and can materially affect our business or financial results	> Quality management systems incorporating monitoring, training and assurance activities > Collaborating with regulatory bodies and advocacy groups to monitor and respond to changes in the regulatory environment, including revised process, timelines and guidance	Unchanged
Secure and protect product IP	Discovering and developing medicines requires a significant investment of resources. For this to be a viable investment, new medicines must be safeguarded from being copied for a reasonable amount of time. If we are not successful in obtaining, maintaining, defending or enforcing our IP rights, our revenues could be materially adversely affected Third parties may allege infringement of their IP, and may seek injunctions and/or damages, which, if ultimately awarded, could adversely impact our commercial and financial performance	> Active management of IP rights and IP litigation	Unchanged
Commercialisation			
Externally driven demand, pricing, access and competitive pressures	Operating in over 100 countries, we are subject to political, socioeconomic and financial factors both globally and in individual countries. There can be additional pressure from governments and other healthcare payers on medicine prices and sales in response to recessionary pressures, reducing our revenue, profits and cash flow	> Focus on Growth Platforms > Demonstrating value of medicines/health economics > Global footprint > Diversified portfolio	Increasing risk Global economic and political conditions placing downward pressure on healthcare pricing and spending, and therefore on revenue
Quality and execution of commercial strategies	If commercialisation of a product does not succeed as anticipated, or its rate of sales growth is slower than anticipated, there is a risk that we may not be able to fully recoup the costs in launching it	> Focus on Growth Platforms > Accelerate and risk share through business development and strategic collaborations and alliances	Increasing risk The number of new product launches is increasing. Maximising the commercial potential of these new products underpins the success of our strategy and the delivery of our short- and medium-term targets
Supply chain and business execution			
Maintain supply of compliant, quality product	Delays or interruptions in supply can lead to recalls, product shortages, regulatory action, reputational harm and lost sales	> Establishment of new manufacturing facilities, creating capacity and technical capability to support new product launches, particularly biologics > Business continuity and resilience initiatives, disaster and data recovery and emergency response plans > Contingency plans including dual sourcing, multiple suppliers and stock levels > Quality management systems	Unchanged

Risk category and Principal Risks	Context/potential impact	Management actions	Trend versus prior year
Supply chain and business execution *continued*			
Information technology, data security and privacy	Significant disruption to our IT systems, cybersecurity incidents including breaches of data security, or data privacy failure, could harm our reputation and materially affect our financial condition or results of operations. This could lead to regulatory penalties or non-compliance with laws and regulations	> Cybersecurity framework and dashboard > Privacy office oversees compliance with data privacy legislation > Disaster and data recovery plans > Strategies to secure critical systems and processes > Regular cybersecurity and privacy training for employees	Growing multi-faceted cyber threat. Tougher legislative environment governs data protection following introduction of new EU GDPR legislation
Attract, develop, engage and retain talented and capable employees at all levels	Failure to attract and retain highly skilled personnel may weaken our succession plans for critical positions in the medium term. Employee uncertainty as a result of, for example, Brexit or organisational change may result in a lower level of employee engagement which could impact productivity and turnover. Both could adversely affect the achievement of our strategic objectives	> Targeted recruitment and retention strategies deployed > Identification and active support of staff potentially impacted by Brexit > Development of our employees > Evolve our culture > Focus on simplification	
Legal, regulatory and compliance			
Safety and efficacy of marketed products	Patient safety is very important to us and we strive to minimise the risks and maximise the benefits of our medicines. Failure to do this could adversely impact our reputation, our business and the results of operations, and could lead to product liability claims	> Robust processes and systems in place to manage patient safety and efficacy trends as well as externally reported risks through regulatory agencies and other parties. This includes a comprehensive pharmacovigilance programme supplemented by close monitoring and review of adverse events	The number of new products in our marketed portfolio is growing and is anticipated to increase further as our pipeline develops. Our ability to accurately assess the safety and efficacy of new products is inherently limited due to relatively short periods of product testing and relatively small clinical study patient samples
Defence of product, pricing and practices litigation	Investigations or legal proceedings could be costly, divert management attention or damage our reputation and demand for our products. Unfavourable resolutions could subject us to criminal liability, fines, penalties or other monetary or non-monetary remedies, adversely affecting our financial results	> Combined internal and external counsel management	
Meet regulatory and ethical expectations on commercial practices, including bribery and corruption, and scientific exchanges	Any failure to comply with applicable laws, rules and regulations, including bribery and corruption legislation, may result in civil and/or criminal legal proceedings and/or regulatory sanctions, fines or penalties, impacting financial results	> Strong ethical and compliance culture > Established compliance framework in place including annual Code of Ethics training for all employees > Focus on due diligence and oversight of third-party engagements	Increasing government and regulatory scrutiny and evolving compliance challenges as complexity of business relationships increases
Economic and financial			
Achieve strategic plans and meet targets and expectations	Failure to successfully implement our business strategy may frustrate the achievement of our financial or other targets or expectations. This failure could, in turn, damage our reputation and materially affect our business, financial position or results of operations	> Focus on Growth Platforms and innovative science in three main therapy areas > Strengthen pipeline through acquisitions, licensing and collaborations > Appropriate capital structure and balance sheet > Portfolio-driven decision making process governed by senior executive-led committees	Increasing challenge to balance long- and short-term investments as we navigate a period of loss of exclusivity on key brands while seeking to maximise the commercial potential of new product launches

Financial Review

2018 marked our return to Product Sales growth with strong performance from Growth Platforms and New Medicines more than offsetting the continued impact from patent expiries.

"Product sales grew 4% to $21.0 billion driven by outstanding performance of our Oncology medicines; Emerging Markets sales continued to grow; and New CVRM grew by 12% (CER:12%)."

In 2018, Product Sales grew 4% to $21.0 billion driven by outstanding performance of our Oncology medicines, which grew 50% (CER: 49%), led by *Tagrisso*, *Lynparza* and *Imfinzi*. Emerging Markets sales continued to grow, especially in China, and it is now our largest region by total Product Sales. New CVRM grew 12% (CER:12%) to $4.0 billion with both *Farxiga* and *Brilinta* delivering sales over $1.3 billion annually. Total Revenue was $22.1 billion, a 2% decline led by lower Externalisation Revenue of $1.0 billion, a 55% reduction from 2017. In 2018, $0.8 billion of Externalisation Revenue was received as part of our collaboration with MSD on *Lynparza* and selumetinib.

Reported R&D expenses increased by 3% as a result of higher intangible asset impairment charges. Core R&D expenses declined by 3% with focus on resource prioritisation, productivity improvements and improved development processes all delivering cost reductions whilst maintaining high levels of activity. Reported SG&A expenses declined by 2% (CER: 3%) primarily due to the decrease in fair value of contingent consideration liabilities. Core SG&A expenses increased by 10% (CER: 9%) due to commercial and medical affairs support for New Medicines and to drive growth in China.

Reported other operating income was $2.5 billion in the year and included income from various disposal transactions, including the sale of the rights to *Nexium* in Europe to Grünenthal and the sale of the rights to *Seroquel* and *Seroquel XR* in UK, China and other international region markets to Luye Pharma.

The Reported tax rate of (3)% and Core tax rate of 11% for the year benefitted from a favourable net adjustment of $0.3 billion to deferred tax, reflecting the recently announced reductions to the Dutch and Swedish income tax rate. Additionally, there was a $0.2 billion benefit to the Reported and Core tax rates resulting from a reduction in tax provisions.

Reported operating profit declined by 8% (CER: 7%) to $3.4 billion and Core operating profit decreased by 17% (CER: 17%) to $5.7 billion in the year. Reported EPS was $1.70 and Core EPS was $3.46.

We generated a net cash inflow from operating activities of $2.6 billion in the year and we maintained a strong, investment-grade credit rating. During the year, we issued new bonds totalling $3.0 billion and repaid $1.4 billion of maturing bonds. We ended the year with total gross debt of $19.1 billion, $6.1 billion of cash, investments and derivatives, with net debt of $13.0 billion.

Marc Dunoyer
Chief Financial Officer

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The purpose of this Financial Review is to provide a balanced and comprehensive analysis of the financial performance of the business during 2018, the cash flow and liquidity position of the business, the financial position as at the end of the year, and the main business factors and trends which could affect the future financial performance of the business.

Business background and results overview

The business background is covered in the Marketplace section from page 11, the Therapy Area Review from page 50 and describes in detail the developments in our products.

As described earlier in this Annual Report, sales of our products are directly influenced by medical need and are generally paid for by health insurance schemes or national healthcare budgets. Our operating results can be affected by a number of factors other than the delivery of operating plans and normal competition, such as:

> The risk of competition from generics following loss of patent protection or patent expiry of one of our products, or an 'at risk' launch by a competitor, or the launch of a competitive product in the same class as one of our products, with potential adverse effects on sales volumes and prices. Details of patent expiries for our key marketed products are included in Patent Expiries of Key Marketed Products from page 217.

> The adverse impact on pharmaceutical prices as a result of the macroeconomic and regulatory environment. For instance, in the US, political leadership has continued to consider drug pricing controls and transparency measures at national and local levels. In other parts of the world, governments have continued to implement and expand price control measures, including reference pricing.

> The timings of new product launches, which can be influenced by national regulators, the speed to market relative to competitor products and the risk that such new products do not succeed as anticipated, together with the rate of sales growth and costs following new product launches.

> Currency fluctuations. Our functional and reporting currency is the US dollar, but we have substantial exposures to other currencies, in particular the Chinese renminbi, euro, Japanese yen, pound sterling and Swedish krona.

> Macro factors such as greater demand from an ageing population and increasing requirements of Emerging Markets.

> Supply chain risks including the failure of third parties to supply timely quality products, such as raw materials, and the risk of catastrophic failure of critical internal processes leading to an inability to research, manufacture or supply products to patients.

Further details of the risks faced by the business are given in Risk Overview from page 70 and Risk from page 220.

Over the longer term, the success of our R&D is crucial and we devote substantial resources to this area. The benefits of this investment are expected to emerge over the long-term and there is considerable inherent uncertainty as to the scale and timing of outcomes and their transition to saleable products.

The most significant features of our financial results in 2018 are:

> Total Revenue down 2% to $22,090 million (CER: 2%). Product Sales were up 4% (CER: 4%) reflecting the performance of New Medicines and the ongoing growth in Emerging Markets.
  - Oncology sales increased by 50% (CER: 49%) with *Tagrisso* up 95% (CER: 93%) to $1,860 million, *Imfinzi* sales reaching $633 million arising primarily in the US and *Lynparza* sales of $647 million representing growth of 118% (CER: 116%), driven by expanded use in the treatment of ovarian cancer and first approval in the treatment of breast cancer.
  - New CVRM sales increased by 12% (CER: 12%) to $4,004 million and included *Farxiga* sales of $1,391 million with growth of 30% (CER: 30%) including a sales increase of 45% (CER: 52%) in Emerging Markets and *Brilinta* sales of $1,321 million representing growth of 22% (CER: 21%).
  - Respiratory was up 4% (CER: 3%) reflecting growth for *Pulmicort* and the success of the 2017 launch of *Fasenra*, offset by a continued fall in US Product Sales of *Symbicort*.
  - Emerging Markets grew by 12% (CER: 13%) to $6,891 million, making it the Group's largest region by Product Sales for the first time. China sales increased by 28% (CER: 25%) to $3,795 million. Oncology sales in China were up 44% (CER: 41%) partly underpinned by the 2017 launch of *Tagrisso*.

> Reported operating profit was down 8% (CER: 7%) to $3,387 million (2017: $3,677 million) driven by declines in Total Revenue and the increase to Reported R&D expenses.

> Core operating profit was also down 17% (CER: 17%) to $5,672 million (2017: $6,855 million). The difference between Core and Reported operating profit is largely driven by the impact of non-core amortisation and impairment of intangibles. The decrease from prior year was driven by a credit to core adjustments from the release of legal provisions.

> Reported operating margin of 15% of Total Revenue was one percentage point down on 2017 (CER: one percentage point). Core operating margin was 26% of Total Revenue (2017: 31%).
> Reported EPS was down 28% (CER: 29%) to $1.70. Core EPS was also down 19% (CER: 19%) to $3.46.
> Dividends paid amounted to $3,484 million (2017: $3,519 million).

Measuring performance

The following measures are referred to in this Financial Review when reporting on our performance both in absolute terms, but more often in comparison to earlier years:

> Reported performance: Reported performance takes into account all the factors (including those which we cannot influence, such as currency exchange rates) that have affected the results of our business, as reflected in our Group Financial Statements prepared in accordance with IFRSs as adopted by the EU and as issued by the IASB (IFRS).
> Non-GAAP financial measures: Core financial measures, EBITDA, Net debt, Ongoing Externalisation Revenue and Initial Externalisation Revenue are non-GAAP financial measures because they cannot be derived directly from the Group Consolidated Financial Statements. Management believes that these non-GAAP financial measures, when provided in combination with Reported results, will provide investors with helpful supplementary information to better understand the financial performance and position of the Group on a comparable basis from period to period. These non-GAAP financial measures are not a substitute for, or superior to, financial measures prepared in accordance with GAAP.
> Core financial measures are adjusted to exclude certain significant items, such as:
  – amortisation and impairment of intangible assets, including impairment reversals but excluding any charges relating to IT assets
  – charges and provisions related to our global restructuring programmes, which include charges that relate to the impact of our global restructuring programmes on our capitalised manufacturing facilities and IT assets
  – other specified items, principally comprising acquisition-related costs and credits, which include fair value adjustments and the imputed finance charge relating to contingent consideration on business combinations, legal settlements and foreign-exchange gains and losses on certain non-structural intra-group loans. In determining the adjustments to arrive at the Core result, we use a set of established principles relating to the nature and materiality of individual items or groups of items, excluding, for example, events which (i) are outside the normal course of business, (ii) are incurred in a pattern that is unrelated to the trends in the underlying financial performance of our ongoing business, or (iii) are related to major acquisitions, to ensure that investors' ability to evaluate and analyse the underlying financial performance of our ongoing business is enhanced. See the 2018 Reconciliation of Reported results to Core results table on the opposite page for a reconciliation of Reported to Core performance, as well as further details of the adjustments.
> EBITDA is defined as Reported Profit before tax plus net finance expense, share of after tax losses of joint ventures and associates and charges for depreciation, amortisation and impairment. Reference should be made to the Reconciliation of Reported Profit Before Tax to EBITDA included on page 78 of this Annual Report.
> Net debt is defined as interest-bearing loans and borrowings net of cash and cash equivalents, other investments and net derivative financial instruments. Reference should be made to the Net debt reconciliation table included on page 82 of this Annual Report.
> Ongoing Externalisation Revenue is defined as Externalisation Revenue excluding Initial Externalisation Revenue (which is defined as Externalisation Revenue that is recognised at the point in time control is transferred). Ongoing Externalisation Revenue comprises, among other items, milestones, profit sharing and royalties. Reference should be made to the Externalisation Revenue table on page 78 of this Annual Report.
> Constant exchange rate (CER) growth rates: These are also non-GAAP measures. These measures remove the effects of currency movements by retranslating the current year's performance at the previous year's average exchange rates and adjusting for other exchange effects, including hedging. A reconciliation of the Reported results adjusted for the impact of currency movements is provided in the 2018 Reported operating profit table on the page opposite.
> Gross and operating margin percentages: These measures set out the progression of key performance margins and illustrate the overall quality of the business.
> Prescription volumes and trends for key products: These measures can represent the real business growth and the progress of individual products better and more immediately than invoiced sales.

We strongly encourage readers of the Annual Report not to rely on any single financial measure but to review our financial statements, including the notes thereto, and our other publicly filed reports, carefully and in their entirety.

CER measures allow us to focus on the changes in revenues and expenses driven by volume, prices and cost levels relative to the prior period. Revenues and cost growth expressed in CER allow management to understand the true local movement in revenues and costs, in order to compare recent trends and relative return on investment. CER growth rates can be used to analyse revenues in a number of ways but, most often, we consider CER growth by products and groups of products, and by countries and regions. CER revenue growth can be further analysed into the impact of revenue volumes and selling price. Similarly, CER cost growth helps us to focus on the real local change in costs so that we can manage the cost base effectively.

We believe that disclosing non-GAAP financial and growth measures, in addition to our Reported financial information, enhances investors' ability to evaluate and analyse the financial performance and trends of our ongoing business and the related key business drivers. The adjustments are made to our Reported financial information in order to show non-GAAP financial measures that illustrate clearly, on a year-on-year or period-by-period basis, the impact on our performance caused by factors such as changes in revenues and expenses driven by volume, prices and cost levels relative to such prior years or periods.

Readers of the Annual Report should note that Core results cannot be achieved without incurring the costs that the Core measures exclude such as:

> Amortisation of intangible assets which generally arise from business combinations and individual licence acquisitions. We adjust for these charges because their pattern of recognition is largely uncorrelated with the underlying performance of the business. However, a significant part of our revenues could not be generated without owning the associated acquired intangible assets.
> Charges and provisions related to our global restructuring programmes which can take place over a significant period of time, given the long life-cycle of our business. We adjust for these charges and provisions because they primarily reflect the financial impact of change to legacy arrangements, rather than the underlying performance of our ongoing business. However, our Core results do reflect the benefits of such restructuring initiatives.

It should also be noted that other costs excluded from our Core results, such as finance charges related to contingent consideration will recur in future years and other excluded items such as impairments and legal settlement costs, along with other acquisition-related costs, may recur in the future.

As shown in the 2018 Reconciliation of Reported results to Core results table to the right, our reconciliation of Reported financial information to Core financial measures includes a breakdown of the items for which our Reported financial information is adjusted, and a further breakdown by specific line item as such items are reflected in our Reported income statement. This illustrates the significant items that are excluded from Core financial measures and their impact on our Reported financial information, both as a whole and in respect of specific line items.

Management presents these results externally to meet investors' requirements for transparency and clarity. Core financial measures are also used internally in the management of our business performance, in our budgeting process and when determining compensation. As a result, Core financial measures merely allow investors to differentiate between different kinds of costs and they should not be used in isolation. Readers should also refer to our Reported financial information in the 2018 Reported operating profit table and our reconciliation of Core financial measures to Reported financial information in the Reconciliation of Reported results to Core results table, both to the right, for our discussion of comparative Actual growth measures that reflect all factors that affect our business.

Our determination of non-GAAP measures, and our presentation of them within this financial information, may differ from similarly titled non-GAAP measures of other companies.

The SET retains strategic management of the costs excluded from Reported financial information in arriving at Core financial measures, tracking their impact on Reported operating profit and EPS, with operational management being delegated on a case-by-case basis to ensure clear accountability and consistency for each cost category.

Results of operations – summary analysis of year ended 31 December 2018

2018 Reported operating profit

	2018			2017	Percentage of Total Revenue		Reported 2018 compared with Reported 2017	
	Reported $m	CER growth $m	Growth due to exchange effects $m	Reported $m	Reported 2018 %	Reported 2017 %	Actual growth %	CER growth[1] %
Product Sales	21,049	733	164	20,152			4	4
Externalisation Revenue	1,041	(1,274)	2	2,313			(55)	(55)
Total Revenue	22,090	(541)	166	22,465			(2)	(2)
Cost of sales	(4,936)	(542)	(76)	(4,318)	(22.3)	(19.2)	14	13
Gross profit	17,154	(1,083)	90	18,147	77.7	80.8	(5)	(6)
Distribution expenses	(331)	(20)	(1)	(310)	(1.5)	(1.4)	7	6
Research and development expenses	(5,932)	(151)	(24)	(5,757)	(26.9)	(25.6)	3	3
Selling, general and administrative expenses	(10,031)	310	(108)	(10,233)	(45.4)	(45.5)	(2)	(3)
Other operating income and expense	2,527	697	–	1,830	11.4	8.1	38	38
Operating profit	3,387	(247)	(43)	3,677	15.3	16.4	(8)	(7)
Net finance expense	(1,281)	(27)	141	(1,395)				
Share of after tax losses of joint ventures and associates	(113)	(58)	–	(55)				
Profit before tax	1,993	(332)	98	2,227			(10)	(14)
Taxation	57	(574)	(10)	641				
Profit for the period	2,050	(906)	88	2,868				
Basic earnings per share ($)	1.70			2.37			(28)	(29)

[1] As detailed on page 76, CER growth is calculated using prior year actual results adjusted for certain exchange effects including hedging.

2018 Reconciliation of Reported results to Core results

	2018 Reported $m	Restructuring costs $m	Intangible amortisation and impairments $m	Diabetes Alliance[4] $m	Other[3] $m	2018 Core[1] $m	Core 2018 compared with Core 2017[1] Actual growth %	CER growth %
Gross profit	17,154	432	187	–	–	17,773	(4)	(4)
Product Sales gross margin %[2]	*76.6*					*79.5*		
Distribution expenses	(331)	–	–	–	–	(331)	7	6
Research and development expenses	(5,932)	94	572	–	–	(5,266)	(3)	(3)
Selling, general and administrative expenses	(10,031)	181	1,582	(60)	(323)	(8,651)	10	9
Other operating income and expense	2,527	(10)	4	–	(374)	2,147	10	10
Operating profit	3,387	697	2,345	(60)	(697)	5,672	(17)	(17)
Operating margin as a % of Total Revenue	*15.3*					*25.7*		
Net finance expense	(1,281)	–	–	337	208	(736)		
Taxation	57	(146)	(487)	(73)	109	(540)		
Basic earnings per share ($)	1.70	0.43	1.47	0.16	(0.30)	3.46	(19)	(19)

[1] Each of the measures in the Core column in the above table is a non-GAAP measure.
[2] Gross margin as a % of Product Sales reflects gross profit derived from Product Sales, divided by Product Sales.
[3] See page 81 for further details of other adjustments.
[4] Relating to the 2014 acquisition of BMS's share of Global Diabetes Alliance.

Total Revenue

Total Revenue for the year was down 2% (CER: 2%) to $22,090 million, comprising Product Sales of $21,049 million up 4% (CER: 4%) and Externalisation Revenue of $1,041 million, a decrease of 55% (CER: 55%).

By Geography

Product Sales in Emerging Markets continued to increase with growth of 12% (CER: 13%) to $6,891 million in 2018, including growth in China of 28% (CER: 25%) to $3,795 million. Sales of *Tagrisso* in Emerging Markets increased by $212 million in the year to $347 million, an increase of 157% (CER: 159%). US Product Sales were up 11% (CER: 11%) to $6,876 million, reflecting the success of the new Oncology medicines and the strong performance of *Fasenra*. In Europe, Product Sales declined by 6% (CER: 10%) to $4,459 million, reflecting the continued impact from generic competition on *Crestor*. Established Markets sales declined 8% (CER: 9%) to $2,823 million with sales in Japan down 9% (CER: 11%) to $2,004 million largely driven by the decline in *Crestor* sales, which declined by 66% (CER: 67%) to $166 million in the year as the impact of generic competition from 2017 took effect.

By Product

Our largest selling products in 2018 were *Symbicort* ($2,561 million), *Tagrisso* ($1,860 million), *Nexium* ($1,702 million) and *Crestor* ($1,433 million). Global sales of *Symbicort* declined by 9% (CER: 10%) with 13% growth in Emerging Markets (CER: 14%) being more than offset by declines in US and Europe due to the impact of a competitive environment on net pricing. *Tagrisso* sales grew by 95% (CER: 93%) reflecting strong market penetration following 2017 approvals in US and China. *Nexium* sales were down 13% (CER: 14%) reflecting continued lower demand as a result of the loss of exclusivity from 2015, however the decline in sales has been slower than expected. *Crestor* sales declined by 39% (CER: 40%) as the impact of generic competition continued to take effect. There were also continued strong performances in the year from *Farxiga* and *Brilinta*, with *Farxiga* growing by 30% (CER: 30%) and *Brilinta* by 22% (CER: 21%).

Reconciliation of Reported Profit Before Tax to EBITDA

	2018 $m	2017 $m	Actual growth %	CER growth %
Reported profit before tax	**1,993**	2,227	**(10)**	**(14)**
Net finance expense	**1,281**	1,395	**(8)**	**2**
Share of after tax losses of joint ventures and associates	**113**	55	**104**	**104**
Depreciation, Amortisation and Impairment	**3,753**	3,036	**24**	**24**
EBITDA	**7,140**	6,713	**6**	**7**

Growth Platforms

	2018 Product Sales $m	2017 Product Sales $m	Actual growth %	CER growth %
Emerging Markets	**6,891**	6,149	**12**	**13**
Respiratory	**4,911**	4,706	**4**	**3**
New CVRM[1]	**4,004**	3,567	**12**	**12**
Japan	**2,004**	2,208	**(9)**	**(11)**
Oncology[2]	**6,028**	4,024	**50**	**49**
Total Growth Platform Product Sales[3]	**18,464**	16,396	**13**	**12**

[1] New Cardiovascular, Renal & Metabolic Diseases, incorporating *Brilinta* and Diabetes.
[2] Oncology comprises total Oncology Product Sales.
[3] Certain Product Sales are included in more than one Growth Platform. Total Growth Platform sales represents the net total sales for all Growth Platforms.

Externalisation Revenue

	2018 $m	2017 $m
Externalisation Revenue – Initial		
Crestor (Almirall)	**61**	–
Lynparza/selumetinib (MSD)	**–**	997
Zoladex (TerSera)	**–**	250
MEDI8897 (Sanofi)	**–**	127
Other	**51**	118
Total Initial Externalisation Revenue	**112**	1,492
Ongoing Externalisation Revenue		
Lynparza/selumetinib (MSD) – option exercised	**400**	250
Lynparza/selumetinib (MSD) – milestone	**390**	–
Zoladex (TerSera) – milestone	**35**	–
Global non-US anaesthetics portfolio (Aspen) – milestone	**–**	150
brodalumab (Valeant) – milestone	**–**	130
AZD3293 (Lilly) – milestone	**–**	50
Royalties	**49**	108
Other	**55**	133
Total Ongoing Externalisation Revenue	**929**	821
Total Externalisation Revenue	**1,041**	2,313

Growth Platforms

In the periods under review, our Growth Platforms included products in our three main therapy areas, and a focus on the Emerging Markets and Japan. Our Growth Platforms grew by 13% (CER: 12%), representing 84% of Total Revenue after removing the effect of certain Product Sales which are included in more than one Growth Platform.

Product Sales in Emerging Markets grew by 12% compared to 2017 (CER: 13%) to $6,891 million partly driven by a strong performance from *Tagrisso* with growth of 157% (CER: 159%). Product Sales in China increased by 28% in 2018 (CER: 25%), representing 55% of Emerging Markets Product Sales in the year.

Product Sales of Respiratory medicines increased by 4% (CER: 3%), with the impact of pricing pressure in the US for *Symbicort* being more than offset by a strong performance by Respiratory in Emerging Markets and higher demand for *Pulmicort* in China.

New CVRM grew by 12% (CER: 12%) with revenue of $4,004 million (2017: $3,567 million). Within New CVRM, sales of *Brilinta* in the year were $1,321 million, an increase of 22% (CER: 21%). *Brilinta* sales in the US were up 16% to $588 million, as it remained the branded oral anti-platelet market leader.

Our Diabetes Product Sales were 8% higher than in 2017, driven primarily by growth of 30% on *Farxiga* (CER: 30%) with global sales of $1,391 million as it continued to be our largest-selling Diabetes medicine and SGLT-2 class growth was supported by growing evidence around cardiovascular benefits, including data from the CVD-REAL study that was published in March 2017.

Japan Product Sales declined by 9% (CER: 11%) with growth on *Tagrisso* and *Forxiga*, outweighed by the impact of the entry of generic competition to *Crestor* in 2017.

Product Sales of Oncology medicines increased to $6,028 million in 2018 (2017: $4,024 million), $1,860 million of which came from *Tagrisso* (2017: $955 million), which continues to be our leading medicine for the treatment of lung cancer and received regulatory approval in more than 55 countries by the end of 2018.

Externalisation Revenue

Details of our significant business development transactions which give rise to Externalisation Revenue are given below:

> In November 2018, AstraZeneca entered into an agreement with Swedish Orphan Biovitrum AB (Sobi) to sell the US rights to *Synagis*. Under the agreement Sobi will also have the right to participate in AstraZeneca's share of US profits and losses related to MEDI8897. The deal was completed on 23 January 2019 and AstraZeneca received an upfront consideration of $1.6 billion, including cash of $966 million and ordinary shares in Sobi with an initial market value of $600 million. This income was recorded in 2019. AstraZeneca will also receive up to $470 million in sales-related payments for *Synagis*, $175 million following the submission of the Biologics License Application (BLA) for MEDI8897, potential net payments of $110 million for other MEDI8897 profit-related milestones and $60 million in non-contingent payments for MEDI8897 during the period from 2019 to 2021.

> In December 2017, AstraZeneca entered into an agreement effective January 2018 with Almirall, under which Almirall is granted an exclusive and perpetual licence to distribute and undertake certain manufacturing activities related to *Crestor* and *Provisacor* in Spain. Almirall made an upfront payment of €51 million on completion of the deal and will pay additional sales-related milestones of up to €55 million plus a royalty for ten years.

> In July 2017, the Group announced a global strategic oncology collaboration with MSD to co-develop and co-commercialise AstraZeneca's *Lynparza* for multiple cancer types. Under the collaboration, the companies will develop and commercialise *Lynparza* jointly, both as monotherapy and in combination with other potential medicines. AstraZeneca and MSD will also jointly develop and commercialise AstraZeneca's selumetinib, an oral, potent, selective inhibitor of MEK, part of the mitogen-activated protein kinase (MAPK) pathway, currently being developed for multiple indications including thyroid cancer. Independently, AstraZeneca and MSD will develop and commercialise *Lynparza* in combination with their respective PD-L1 and PD-1 medicines, *Imfinzi* and *Keytruda*. Under the terms of the agreement, the two companies will share the development and commercialisation costs for *Lynparza* and selumetinib monotherapy and non-PD-L1/PD-1 combination therapy opportunities. Gross profits from *Lynparza* and selumetinib Product Sales generated through monotherapies or combination therapies will be shared equally. MSD will fund all development and commercialisation costs of *Keytruda* in combination with *Lynparza* or selumetinib. AstraZeneca will fund all development and commercialisation costs of *Imfinzi* in combination with *Lynparza* or selumetinib. AstraZeneca will continue to manufacture *Lynparza* and selumetinib. As part of the agreement, MSD will pay AstraZeneca up to $8.5 billion in total consideration, including $1.6 billion upfront, $750 million for certain licence options and up to $6.2 billion contingent upon successful achievement of future regulatory and sales milestones. Of the upfront payment of $1.6 billion, $1.0 billion was recognised as Externalisation Revenue on deal completion in 2017, with the remaining $0.6 billion deferred to the balance sheet. AstraZeneca will book all Product Sales of *Lynparza* and selumetinib; gross profits due to MSD under the collaboration will be recorded under Cost of Sales.

> In November 2017, MSD exercised the first licence option resulting in Externalisation Revenue of $250 million.

> In January 2018, the FDA expanded the approved use of *Lynparza* to include the treatment of patients with certain types of breast cancer. The approval triggered a $70 million milestone payment from MSD to AstraZeneca.

> In June 2018, net sales of *Lynparza* reached $250 million cumulative sales threshold, triggering a sales-related milestone of $100 million to fall due to AstraZeneca.

> In November 2018, MSD exercised the second licence option resulting in Externalisation Revenue of $400 million. In addition to the exercise of this option, net sales of *Lynparza* reached the $500 million cumulative sales threshold, triggering a sales-related milestone of $150 million to fall due to AstraZeneca.

> In December 2018, AstraZeneca was notified of an FDA approval of *Lynparza*, which triggered the SOLO-1 $70 million milestone payment to AstraZeneca.

> In March 2017, AstraZeneca announced an agreement to develop and commercialise MEDI8897 jointly with Sanofi. Under the terms of the global agreement, Sanofi made an upfront payment of €120 million and will pay up to €495 million upon achievement of certain development and sales-related milestones. All costs and profits are shared equally. The US element of this collaboration is the subject of a participation agreement with Sobi, entered into in November 2018 and effective 23 January 2019.

> In March 2017, AstraZeneca entered into an agreement with TerSera for the commercial rights to *Zoladex* in the US and Canada. TerSera paid $250 million upon completion of the transaction. The Group will also receive sales-related income through milestones totalling up to $70 million, as well as recurring quarterly sales-based payments at mid-teen percent of Product Sales. AstraZeneca will also manufacture and supply *Zoladex* to TerSera, providing a further source of ongoing income from *Zoladex* in the US and Canada. In December 2018, TerSera paid a sales-related milestone of $35 million to AstraZeneca.
> In October 2016, the Group announced an agreement with Aralez for the rights to the branded and authorised generic (marketed by Par Pharmaceuticals) for *Toprol-XL* (metoprolol succinate) in the US. Aralez paid $175 million upon completion of the transaction. Aralez will also pay up to $48 million in milestone and sales-related payments, as well as mid-teen percentage royalties on Product Sales. AstraZeneca continues to manufacture and supply *Toprol-XL* and the authorised generic medicine to Aralez. In May 2018, Aralez announced a change in strategic direction and the closure of their US commercial operations and this was followed shortly afterwards by an announcement that they had formally moved in bankruptcy proceedings. A provision of $14 million has been recorded for overdue receivables.
> In June 2016, AstraZeneca announced that it had entered into a commercialisation agreement with Aspen for rights to its global anaesthetics portfolio outside the US. The agreement covers seven established medicines – *Diprivan*, *EMLA* and five local anaesthetics (*Xylocaine*, *Marcaine*, *Naropin*, *Carbocaine* and *Citanest*). Under the terms of the agreement, Aspen acquired the commercialisation rights for an upfront consideration of $520 million. In July 2017, Aspen achieved the first Product Sales related payment milestone triggering a payment to AstraZeneca of $150 million. In September 2017, AstraZeneca announced that it had entered into an agreement with Aspen, under which Aspen acquired the residual rights to the seven established anaesthetics medicines. This new agreement completed in October 2017 and income under this arrangement is now recorded in Other operating income and expense, in line with our definition of Externalisation Revenue in the Accounting Policy note on page 155.
> In February 2016, the Group entered into a licensing agreement with CMS for the commercialisation rights in China to *Plendil* (felodipine). Under the terms of the agreement, CMS paid AstraZeneca $310 million for the licence ($155 million in 2016 and a further $155 million in 2017).
> In September 2015, AstraZeneca announced that the Group had entered into a collaboration agreement with Valeant under which AstraZeneca granted an exclusive licence to Valeant to develop and commercialise brodalumab, except in Japan and certain other Asian countries. Valeant assumed all development costs associated with the regulatory approval for brodalumab. Under the terms of the agreement, Valeant made an upfront payment to AstraZeneca of $100 million in 2015. The agreement also included pre-launch milestones of up to $170 million and further sales-related milestone payments of up to $175 million. After approval, profits would be shared between Valeant and AstraZeneca. In February 2017, the FDA approved brodalumab injection for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy and have failed to respond or lost response to other systemic therapies, triggering a milestone payment of $130 million to AstraZeneca.

As detailed in Risk from page 220, the development of any pharmaceutical product candidate is a complex and risky process that may fail at any stage in the development process due to a number of factors (including items such as failure to obtain regulatory approval, unfavourable data from key studies, adverse reaction to the product candidate or indications of other safety concerns). The potential future milestones quoted above are subject to these risks.

Gross margin, operating margin and earnings per share

Reported gross profit declined by 5% (CER: 6%) to $17,154 million. Core gross profit declined by 4% (CER: 4%) to $17,773 million. The declines primarily reflected the lower level of Externalisation Revenue and an adverse impact from an increase in the Cost of Sales. The difference between Reported and Core Gross Margin arose predominantly on the $0.3 billion restructuring costs associated with the impairment of site-related assets and inventory from the US Biologics site closures in Longmont and Boulder, CO.

Reported R&D expenses in the year increased by 3% (CER: 3%) to $5,932 million as a result of increased intangible asset amortisation and impairment. Intangible asset impairment charges of $539 million were recorded following analysis of relevant clinical trial data. Core R&D expenses declined by 3% to $5,266 million reflecting the continued focus on resource prioritisation and productivity improvements.

Reported SG&A expenses decreased by 2% (CER: 3%) to $10,031 million primarily due to the revaluation of contingent consideration liabilities arising on business combinations. Core SG&A expenses increased by 10% (CER: 9%) to $8,651 million reflecting investment in the launch of new medicines.

Reported Other operating income and expense in the year was up 38% (CER: 38%) at $2,527 million which includes $695 million from the sale of the rights to *Nexium* in Europe to Grünenthal, $527 million on the sale of the rights to *Seroquel* and *Seroquel XR* in UK, China and other international region markets to Luye Pharma, $210 million from the sale of rights to *Atacand* in Europe to Cheplapharm, milestone receipts of $172 million from the disposal of the anaesthetics portfolio outside the US to Aspen, and $139 million from the sale of global rights to *Alvesco*, *Omnaris* and *Zetonna* to Covis. As these elements of our income arose from product divestments, where we no longer retain significant ongoing economic interest, in accordance with our Externalisation Revenue definition in the Accounting Policy note on page 155 and the requirements of IFRS 15 'Revenue from Contracts with Customers', proceeds from these divestments are recorded as other operating income.

Reported operating profit declined by 8% (CER: 7%) to $3,387 million in the year. The Reported operating margin declined by one percentage point (CER: one percentage point) to 15% of Total Revenue. The decrease was primarily driven by declines in Total Revenue and Reported gross margin as well as the aforementioned increase in Reported R&D expenses. Core operating profit declined by 17% (CER: 17%) in the year to $5,672 million. The Core operating profit margin decreased by five percentage points to 26% of Total Revenue.

Reported net finance expense decreased by 8% (CER: increased 2%) in the year to $1,281 million (2017: $1,395 million) reflecting the effect of higher Net debt and an adverse movement in the fair value of bonds and derivative instruments and offset by lower levels of discount unwind on Acerta Pharma liabilities. Core net finance expense increased by 13% (CER: 11%) in the year to $736 million.

Reported profit before tax declined by 10% (CER: 14%) in the year to $1,993 million (2017: $2,227 million), reflecting the lower level of Externalisation Revenue, lower Reported gross margin and the increase in Reported R&D expenses. Pre-tax adjustments to arrive at Core profit before tax amounted to $2,830 million in 2018 (2017: $3,923 million), comprising $2,285 million adjustments to operating profit (2017: $3,178 million) and $545 million to net finance expense (2017: $745 million). EBITDA increased by 6% (CER: 7%) to $7,140 million.

Excluded from Core results were:

> Restructuring expenses totalling $697 million (2017: $807 million) were largely driven by $252 million fixed asset impairment and $75 million inventory write off resulting from the announcement of the US Biologics site closures in Longmont and Boulder, CO.
> Amortisation totalling $1,663 million (2017: $1,319 million) relating to intangible assets, except those related to IT and to our acquisition of BMS's share of our Global Diabetes Alliance (which are separately detailed below). Further information on our intangible assets is contained in Note 9 to the Financial Statements from page 169.
> Intangible impairment charges of $683 million (2017: $488 million) excluding those related to IT. Further details relating to intangible asset impairments are included in Note 9 to the Financial Statements from page 169.
> Costs associated with our acquisition of BMS's share of our Global Diabetes Alliance in February 2014 amounting to $277 million (2017: $954 million) and included a fair value credit of $482 million, amortisation charges of $422 million and discount unwinds in Sweden and US of $337 million.
> Other charges which includes net legal provisions amounted to a credit of $489 million (2017: $355 million) and was primarily driven by a $352 million settlement of legal action in Canada in relation to patent infringement of *Losec/Prilosec*, recognised in other income. Further details of legal proceedings in which we are currently involved are contained within Note 29 to the Financial Statements from page 194.
> Also included in other charges are a $208 million discount unwind charge (2017: $305 million) and a $126 million credit (2017: $309 million) for net fair value adjustments relating to contingent consideration and the Acerta Pharma put option arising on our other business combinations as detailed in Note 19 to the Financial Statements from page 177.
> Additionally in 2017 a one-off adjustment of $617 million reflecting adjustments to deferred tax in line with the reduction to the US federal tax rate.

Reported EPS of $1.70 in the year represented a decline of 28% (CER: 29%). The performance was driven by a decline in Externalisation Revenue and increased Cost of Sales, partly offset by an increase in other operating income and expense. Core EPS in the year declined by 19% (CER: 19%) to $3.46.

The Reported tax rate of (3)% and the Core tax rate in the year of 11% benefited from a favourable adjustment of $297 million to deferred taxes, reflecting the recently-announced reductions in Dutch and Swedish corporate income tax rates and a $188 million benefit from reductions of tax provisions. Excluding these benefits, both the Reported and Core tax rates would have been 21%. The income tax paid for the year was $537 million (27% of Reported profit before tax). This was $594 million higher than the tax charge for the year as a result of certain items with no cash impact including $297 million deferred tax credit reflecting the reduction in Dutch and Swedish income tax rates, $509 million of other deferred tax credits, $188 million provision releases relating to the expiry of the statute of limitations and on the conclusion of tax authority review, other net increases in provisions for tax contingencies, partially offset by refunds following a previously disclosed agreement of inter-government transfer pricing arrangements and other cash tax timing differences. We pay corporate income taxes, customs duties, excise taxes, stamp duties, employment and many other business taxes in all jurisdictions where applicable. In addition, we collect and pay employee taxes and indirect taxes such as value added tax. The taxes we pay and collect represent a significant contribution to the countries and societies in which we operate.

Total comprehensive income decreased by $2,516 million from the prior year, resulting in a net income of $991 million for 2018. The decrease in other comprehensive income included foreign exchange losses arising on designating borrowings in net investment hedges of $520 million (2017: gains of $505 million), foreign exchange losses arising on consolidation of $449 million (2017: gains of $536 million) and net losses on equity investments measured at fair value through other comprehensive income of $171 million (2017: $nil), offset by a gain on fair value movements on cash flow hedges transferred to profit and loss of $111 million (2017: $315 million).

Restructuring

Since 2007, we have undertaken significant efforts to restructure and reshape our business to improve our long-term competitiveness. The first phases of this restructuring, involving the integration of MedImmune, efficiencies within the R&D function and a reduction in SG&A costs, were completed in 2011. The targeted commercial restructuring announced in 2015 has also been successfully completed with a total cost of $151 million.

In 2016, we announced plans to advance our strategy through sharper focus by streamlining operations, primarily in Commercial and Manufacturing, to redeploy investment to key therapy areas, particularly Oncology. Restructuring costs associated with this programme were initially forecast to be $1.5 billion by the end of 2017 and generate net annualised benefits of $1.1 billion by 2018. The total cost estimate is now $1.3 billion to be incurred by the end of 2019, with benefits expected to be $1.1 billion in 2019. In addition to the 2016 plan, there are two further active programmes. The first is the continuation of the Phase 3 restructuring that was announced in 2012, superseded by Phase 4 in 2013 and subsequently expanded in 2014. This initiative consists of centralisation of our global R&D footprint into three strategic centres, transformation of the IT organisation, closure of a number of manufacturing facilities and other activities to simplify and streamline the organisation. At the time of the announcement, the Phase 4 programme was estimated to incur $3.2 billion of costs and deliver $1.1 billion of annualised benefits by 2016. By the end of 2018, the Phase 4 programme had incurred costs of $3.5 billion, creating headroom for investment in our pipeline and launch capability. The Phase 4 programme is now expected to complete in 2021, with total programme costs estimated to be $3.7 billion and annualised benefits of $1.2 billion.

The second step was initiated in 2016 and relates to multi-year transformation programmes within our G&A functions (principally Finance and HR) with anticipated costs by the end of 2018 of $270 million. We expect these transformation programmes to deliver annualised benefits of $100 million by the end of 2019. By the end of 2018, these programmes had incurred costs of $304 million with total expected costs rising to $376 million.

The aggregate restructuring charge incurred in 2018 across all our restructuring programmes was $697 million (2017: $807 million), including the US Biologics site closures at Longmont and Boulder, CO, and other acquired assets. Final estimates for programme costs, benefits and headcount impact in all functions are subject to completion of the requisite consultation in the various areas.

Our priority as we undertake these restructuring initiatives is to work with our affected employees on the proposed changes, acting in accordance with relevant local consultation requirements and employment law.

Brexit readiness preparations and planning

Following the UK referendum outcome in June 2016 for the UK to leave the EU, the UK Government and European Commission have been negotiating the terms on which the UK would leave the EU and the framework for the future relationship. While a draft Withdrawal Agreement has been agreed between the UK government and the EU, at this time it remains unclear whether this will be ratified by the UK parliament in its current form, amended or if the UK will leave the EU without a deal. In the absence of a ratified agreement, it is unclear what trading relationships the UK will have with the EU and other significant trading partners after 29 March 2019 given the range of political and legal options. Until the Brexit negotiation process is completed, it is difficult to anticipate the potential impact on our market share, sales, profitability, cashflows and results of operations.

In response to this situation, the Group has taken the decision to implement appropriate actions to mitigate where possible the potential risk of disruption to the supply of medicines (including potential new medicines currently undergoing clinical trials) including, but not limited to, duplication of release testing and procedures for products based in the EU27 and the UK, transfer of regulatory licences, customs and duties set up for introduction or amendment of existing tariffs or processes and associated IT systems reconfiguration. In addition, the Group has engaged with its major suppliers to assess their readiness and continues to work with them to mitigate the risk of disruption to supply chains.

The costs associated with this and certain other actions directly related to Brexit will be charged as restructuring with the majority of such costs expected to be cash costs. The current estimate of these costs is around $40 million. However, until the Brexit process is concluded by the UK and EU parliaments and the impacts of transition to any new arrangement between them are known with clarity, it is difficult to anticipate the overall potential impact on the Group's operations and hence the final expected costs to be incurred.

Cash flow and liquidity – for the year ended 31 December 2018

Summary cash flows

	2018 $m	2017 $m	2016 $m
Net debt brought forward at 1 January	**(12,679)**	(10,657)	(7,762)
Profit before tax	**1,993**	2,227	3,552
Sum of changes in interest, depreciation, amortisation, impairment, and share of after tax losses on joint ventures and associates	**5,147**	4,486	3,707
Movement in working capital and short-term provisions	**(639)**	(50)	926
Tax paid	**(537)**	(454)	(412)
Interest paid	**(676)**	(698)	(677)
Gains on disposal of intangible assets	**(1,885)**	(1,518)	(1,301)
Fair value movements on contingent consideration arising from business combinations	**(495)**	109	(1,158)
Non-cash and other movements	**(290)**	(524)	(492)
Net cash inflow from operating activities	**2,618**	3,578	4,145
Disposal/(purchase) of intangibles (net)	**2,010**	1,082	559
Non-contingent payments on business combinations	**–**	(1,450)	(2,564)
Payment of contingent consideration from business combinations	**(349)**	(434)	(293)
Other capital expenditure (net)	**(1,218)**	(1,319)	(1,405)
Investments	**443**	(2,121)	(3,703)
Dividends	**(3,484)**	(3,519)	(3,561)
Share proceeds	**34**	43	47
Distributions	**(3,450)**	(3,476)	(3,514)
Other movements	**65**	(3)	177
Net debt carried forward at 31 December	**(13,003)**	(12,679)	(10,657)

Net debt reconciliation

	2018 $m	2017 $m	2016 $m
Cash and cash equivalents	**4,831**	3,324	5,018
Other investments[1,2]	**895**	1,300	898
Cash and investments	**5,726**	4,624	5,916
Overdraft and short-term borrowings	**(755)**	(845)	(451)
Finance leases	**–**	(5)	(93)
Current instalments of loans	**(999)**	(1,397)	(1,769)
Loans due after one year	**(17,359)**	(15,560)	(14,495)
Loans and borrowings	**(19,113)**	(17,807)	(16,808)
Net derivative financial instruments	**384**	504	235
Net debt	**(13,003)**	(12,679)	(10,657)

[1] Other investments in 2018 include $46 million (2017: $70 million) of non-current Treasury investments.
[2] Other investments include non-current investments, which are included within the balance of $833 million (2017: $933 million) in the Statement of Financial Position on page 150. The equivalent GAAP measure to Net debt is 'liabilities arising from financing activities', which excludes the amounts for cash and overdrafts, other investments and non-financing derivatives shown above and includes the Acerta Pharma put option of $1,838 million (2017: $1,823 million) shown in non-current other payables.

Bonds issued in 2018 and 2017

	Repayment dates	Face value of bond $m	Net book value of bond at 31 December $m
Bonds issued in 2018:			
3.5% USD bond	2023	850	**845**
Floating rate USD notes	2023	400	**400**
4% USD bond	2029	1,000	**992**
4.375% USD bond	2048	750	**736**
Total 2018		3,000	**2,973**
Bonds issued in 2017:			
2.375% USD bond	2022	1,000	**994**
Floating rate USD notes	2022	250	**250**
3.125% USD bond	2027	750	**743**
Total 2017		2,000	**1,987**

Cash flow and liquidity

Net cash generated from operating activities was $2,618 million in the year ended 31 December 2018, compared with $3,578 million in 2017. The 2018 operating cash inflows reflected the increase in the movement of working capital and short-term provisions impacted by the reduction of provisions relating to legal settlements, as well as launch support for new medicines.

Net investment cash inflows were $443 million (2017: outflow of $2,121 million).

Investment cash outflows for 2018 include $349 million (2017: $434 million) of payments against contingent consideration arising on business combinations and $328 million (2017: $294 million) for the purchase of other intangible assets. 2017 investment cash outflows included a $1,450 million payment to the shareholders of Acerta Pharma, a contractual obligation triggered by the first regulatory approval for *Calquence*, following on from our majority investment in Acerta Pharma in 2016.

Investment cash inflows include $2,338 million (2017: $1,376 million) from the sale of intangible assets, including $700 million on sale of *Nexium* rights in Europe to Grünenthal, $482 million relating to the 2017 sale of our remaining anaesthetic portfolio to Aspen, $354 million on the sale of *Alvesco*, *Omnaris* and *Zetonna* rights outside the US to Covis Pharma, $275 million from the sale of UK, China and other international regions rights to *Seroquel XR* and *Seroquel* IR to Luye Pharma and $205 million from the sale of European rights to *Atacand* to Cheplapharm. The comparative period in 2017 included $300 million from the disposal of EU rights for *Seloken*, $200 million from the divestment of *Zomig* rights outside Japan, $200 million relating to the sale of our remaining anaesthetic portfolio to Aspen and $175 million regarding the *Zavicefta* divestment to Pfizer.

Net cash distributions to shareholders were $3,450 million (2017: $3,476 million), including dividends of $3,484 million (2017: $3,519 million). Proceeds from the issue of shares on the exercise of share options amounted to $34 million (2017: $43 million).

In August 2018, we issued $3.0 billion of bonds in the US dollar debt capital markets with maturities of five, ten and 30 years and repaid a $1.0 billion 1.75% bond and a $0.4 billion floating rate bond, both of which matured in November 2018.

At 31 December 2018, outstanding gross debt (interest-bearing loans and borrowings) was $19,113 million (2017: $17,807 million). Of the gross debt outstanding at 31 December 2018, $1,754 million is due within one year (2017: $2,247 million). Net debt at 31 December 2018 was $13,003 million, compared to $12,679 million at the beginning of the year, as a result of the cash flows as described above. At 31 December 2018, cash, cash equivalents and liquid investments totalled $4.8 billion and undrawn committed cash facilities totalled $4.1 billion.

Financial position – 31 December 2018

All data in this section is on a Reported basis.

Summary statement of financial position

	2018 $m	Movement $m	2017 $m	Movement $m	2016 $m
Property, plant and equipment	**7,421**	**(194)**	7,615	767	6,848
Goodwill and intangible assets	**33,666**	**(4,347)**	38,013	(1,231)	39,244
Assets held for sale	**982**	**982**	–	–	–
Inventories	**2,890**	**(145)**	3,035	701	2,334
Trade and other receivables	**6,089**	**233**	5,856	382	5,474
Trade and other payables	**(19,611)**	**(130)**	(19,481)	493	(19,974)
Provisions	**(891)**	**577**	(1,468)	(50)	(1,418)
Net income tax payable	**(957)**	**(131)**	(826)	128	(954)
Net deferred tax liabilities	**(907)**	**899**	(1,806)	1,048	(2,854)
Retirement benefit obligations	**(2,511)**	**72**	(2,583)	(397)	(2,186)
Non-current other investments (excluding Treasury investments of $46m in 2018 (2017: $70m))	**787**	**(76)**	863	150	713
Investment in associates and joint ventures	**89**	**(14)**	103	4	99
Net debt	**(13,003)**	**(324)**	(12,679)	(2,022)	(10,657)
Net assets	**14,044**	**(2,598)**	16,642	(27)	16,669

Property, plant and equipment

In 2018, Property, plant and equipment decreased by $194 million to $7,421 million. Additions of $1,034 million (2017: $1,311 million) were offset by depreciation of $614 million (2017: $624 million), impairments of $291 million (2017: $78 million), exchange adjustments of $301 million (2017: $352 million) and disposals and other movements of $22 million (2017: $194 million).

Business combinations

In 2016, we acquired a majority equity stake in Acerta Pharma. No business acquisitions were made in 2018 or 2017. Further details of our business combinations are contained in Note 26 to the Financial Statements from page 186.

Goodwill and intangible assets

Our goodwill of $11,707 million (2017: $11,825 million) principally arose on the acquisition of MedImmune in 2007, the restructuring of our US joint venture with MSD in 1998 and the acquisition of BMS's share of the Global Diabetes Alliance.

Intangible assets amounted to $21,959 million at 31 December 2018 (2017: $26,188 million). The decrease was mainly driven by amortisation in the year of $2,165 million (2017: $1,829 million) and the reclassification of assets held for sale of $982 million in respect of *Synagis*. Intangible asset additions were $513 million in 2018 (2017: $441 million). Impairment charges in the year amounted to $683 million (2017: $491 million) including impairments on MEDI0680 and *Eklira*. Disposals of intangible assets totalled $339 million in the year (2017: $307 million).

Further details of our additions to intangible assets, and impairments recorded, are included in Note 9 to the Financial Statements from page 169.

Receivables, payables and provisions

Trade and other receivables decreased by $233 million with trade receivables increasing by $193 million to $2,995 million principally as a result of higher invoiced sales in the US.

Trade and other payables increased by $130 million in 2018 to $19,611 million. The increase was due to higher rebates in the US and China, partially offset by a deferred income release on the *Lynparza* and selumetinib collaboration.

The decrease in provisions of $577 million in 2018 included a $456 million reduction on legal provisions and a $132 million reduction to severance provisions. Further details of the charges made against provisions are contained in Notes 20 and 29 to the Financial Statements on page 178 and from page 194, respectively.

Contingent consideration

The majority of our business acquisitions have included elements of consideration that are contingent on future development and/or sales milestones, with both the Diabetes and Respiratory acquisitions in 2014 also including royalty payments linked to future revenues. The acquisitions of ZS Pharma in 2015 and Acerta Pharma in 2016 had no contingent consideration element and there were no relevant acquisitions in 2017 and 2018.

Our agreement with BMS provides for $0.6 billion in milestones and various sales-related royalty payments up until 2025. Our transaction with Almirall includes further payments of up to $0.6 billion for future development, launch, and various other sales-related milestone payments, and sales-related royalty payments as detailed in Note 19 to the Financial Statements from page 177.

All these future payments are treated as contingent consideration liabilities, and are fair valued using decision-tree analyses, with key assumptions, including the probability of success, the potential for delays and the expected levels of future revenues. The fair value is updated at each reporting date to reflect our latest estimate of the probabilities of these key assumptions. Given the long-term nature of the liabilities, the fair value calculation includes the discounting of future potential payments to their present value using discount rates appropriate to the period over which payments are likely to be made. Over time, as the target date of a consideration payment approaches, the discount in absolute terms of such future potential payment to its present value decreases. Therefore, in each period we take a corresponding charge reflecting the passage of time. We refer to this charge as 'discount unwind'. The calculation of the fair value is considered to be a key estimate.

Both the discount unwind and any movements of the fair value of the underlying future payments can result in significant income statement movements. As detailed in the Results of operations section above, these movements are treated as non-Core items in our income statement analysis. In 2018, we recorded an interest charge of $416 million on the discount unwind on contingent consideration arising on our business combinations, and a net fair value decrease on contingent consideration of $495 million (which resulted in a credit to our income statement for the same amount) driven, principally, by revised forecasts for revenues for our Diabetes franchise. At 31 December 2018, our contingent consideration liability was $5,106 million (2017: $5,534 million) with the movements of the balance detailed in the table to the right.

Tax payable and receivable

Net income tax payable has increased by $131 million (2017: decrease of $128 million) to $957 million, principally due to the receipt of cash in the year following a previously disclosed agreement of inter-government transfer pricing arrangements and other cash tax timing differences, offset by tax provision releases following expiry of statute of limitations and on conclusion of tax authority review. The tax receivable balance of $207 million (2017: $524 million) principally relates to cash tax timing differences.

Net deferred tax liabilities decreased by $899 million (2017: $1,048 million) in the year mainly reflecting adjustments to deferred tax arising from the Dutch and Swedish income tax rate reductions and deferred tax associated with movements in intangible assets. The decrease in net deferred tax liabilities in 2017 reflected adjustments to deferred taxes in line with the reduction to the US federal income tax rate from 35% to 21% and recognition of previously unrecognised deferred tax assets. Additional information on the movement in deferred tax balances is contained in Note 4 to the Financial Statements from page 163.

Retirement benefit obligations

In terms of the Group's major defined benefit plans, approximately 91% of our total retirement defined benefit obligations (or around 80% of net obligations) are concentrated in the UK, the US and Sweden. The UK and US are now largely legacy arrangements as they have been closed to new entrants since 2000. In line with local regulations the collectively bargained Swedish plan is still open to employees born before 1979.

Net retirement benefit obligations decreased by $72 million in 2018 (2017: increase of $397 million) to $2,511 million. Net re-measurement adjustments of $46 million arose principally from higher discount rate assumptions in the UK and US driven by rises in long-term bond yields which lowered the present value of the liabilities, offset by lower than expected investment performance and lower discount rate assumptions in Sweden, where bond yields have fallen. A positive $124 million impact of exchange rate movements also arose in the year as the US dollar strengthened against pound sterling and Swedish krona, reducing liability obligations in US dollar terms. Employer contributions to the pension schemes of $174 million also contributed to the reduction in the net retirement benefit obligation. Benefits paid amounted to $620 million (2017: $581 million).

In the UK, a High Court judgement issued on 26 October 2018 relating to Guaranteed Minimum Pensions (GMPs) is expected to create a precedent for other UK defined benefit pension schemes and therefore is expected to increase the liabilities of the UK Pension Fund. The ruling requires the equalisation of member benefits to address

Contingent consideration arising on business combinations

	2018			2017		
	Acquisition of BMS's share of Diabetes Alliance $m	**Other business combinations $m**	**Total 2018 $m**	Acquisition of BMS's share of Diabetes Alliance $m	Other business combinations $m	Total 2017 $m
At 1 January	**4,477**	**1,057**	**5,534**	4,240	1,217	5,457
Settlements	**(349)**	**–**	**(349)**	(284)	(150)	(434)
Fair value adjustments	**(482)**	**(13)**	**(495)**	208	(99)	109
Discount unwind	**337**	**79**	**416**	313	89	402
At 31 December	**3,983**	**1,123**	**5,106**	4,477	1,057	5,534

Payments due by period

	Less than 1 year $m	**1-3 years $m**	**3-5 years $m**	**Over 5 years $m**	**Total 2018 $m**	Total 2017 $m
Bank loans and other borrowings[1]	**2,403**	**4,233**	**3,882**	**17,405**	**27,923**	25,879
Finance leases	**–**	**–**	**–**	**–**	**–**	5
Operating leases	**188**	**261**	**99**	**136**	**684**	614[2]
Contracted capital expenditure	**625**	**–**	**–**	**–**	**625**	570
Total	**3,216**	**4,494**	**3,981**	**17,541**	**29,232**	27,068

[1] Bank loans and other borrowings include interest charges payable in the period, as detailed in Note 27 to the Financial Statements on page 188.

[2] The Group has revised the presentation of operating leases from 2017 to include operating leases that have been identified during the transition to IFRS 16 as having previously been omitted from this disclosure. This resulted in an increase in 2017 from $523 million to $614 million.

gender inequality in instances where GMP benefits are currently unequal. The estimated impact based on the broad profile of the UK Pension Fund results in a past service cost of £17 million ($23 million) and has been recognised in the income statement for 2018.

The Group has undertaken several initiatives to reduce our net defined benefit pension obligation exposure and manage the associated long-term financial risks. As well as paying cash contributions when required, in the UK, a freeze on pensionable pay has been in effect from 30 June 2010. In the US, both the qualified and non-qualified US pension plans were closed to future accrual in December 2017. Furthermore, liability management exercises have been carried out in the UK, including a Pension Increase Exchange exercise in 2016/2017 along with improvements to the 'at retirement' process to better support members in their retirement decisions.

Further details of our accounting for post-retirement benefit plans are included in Note 21 to the Financial Statements from page 178.

Commitments and contingencies

We have commitments and contingencies which are accounted for in accordance with the accounting policies described in the Financial Statements in the Group Accounting Policies section from page 153.

We also have taxation contingencies. These are described in the Taxation section in the Critical accounting policies and estimates section on page 90 and in Note 29 to the Financial Statements from page 194.

Off-balance sheet transactions and commitments

We have no off-balance sheet arrangements and our derivative activities are non-speculative. The table on page 84 sets out our minimum contractual obligations at the year end.

Research and development collaboration payments

Details of future potential R&D collaboration payments are also included in Note 29 to the Financial Statements on page 194. As detailed in Note 29, payments to our collaboration partners may not become payable due to the inherent uncertainty in achieving the development and revenue milestones linked to the future payments. We may enter into further collaboration projects in the future that may include milestone payments and, therefore, as certain milestone payments fail to crystallise due to, for example, development not proceeding, they may be replaced by potential payments under new collaborations.

Investments, divestments and capital expenditure

We have completed over 260 major or strategically important business development transactions over the past three years, one of which was accounted for as business acquisitions under IFRS 3 'Business Combinations', being the majority investment in Acerta Pharma in 2016.

In addition to the business development transactions detailed under Externalisation Revenue from page 79 of this Financial Review, the following significant collaborations remain in the development phase:

> In April 2015, we entered into two oncology agreements with Innate Pharma: firstly, a licence which provides us with exclusive global rights to co-develop and commercialise IPH2201 in combination with *Imfinzi* and, secondly, an option to license exclusive global rights to co-develop and commercialise IPH2201 in monotherapy and other combinations in certain treatment areas. Under the terms of the combination licence, we assumed exclusive global rights to research, develop and commercialise IPH2201 in combination with *Imfinzi*. We jointly fund Phase II studies with Innate Pharma and we lead the execution of these studies. Under the terms of the agreements, we made an initial payment to Innate Pharma of $250 million, which included the consideration for exclusive global rights to co-develop and commercialise IPH2201 in combination with *Imfinzi*, as well as access to IPH2201 in monotherapy and other combinations in certain treatment areas. The agreement includes a Phase III initiation milestone of $100 million, as well as additional regulatory and sales-related milestones. We record all sales and will pay Innate Pharma double digit royalties on net sales. The arrangement includes the right for Innate Pharma to co-promote in Europe for a 50% profit share in the territory.

> In October 2018, we exercised our option over IPH2201, and simultaneously entered into a further multi-element transaction with Innate Pharma. Under the agreement, we paid $50 million to collaborate on, and acquire an option to license, IPH5201, a first-in-class anti-CD39 mAb. Additionally, we paid $20 million to acquire options over four future programmes currently being developed by Innate Pharma, and paid €62.6 million to acquire a 9.8% stake in Innate Pharma. The $100 million option fee and $50 million have been capitalised as intangible assets, along with the premium paid over market price for the investment in Innate Pharma. The payment for future programmes will be expensed as research and development expenditure over four years. At the same time, we licensed the EU and US rights to *Lumoxiti* to Innate Pharma for $50 million upfront plus future milestone payments of up to $25 million.

> In July 2013, we entered into a strategic collaboration with FibroGen to develop and commercialise roxadustat (FG-4592), a first-in-class oral compound in late-stage development for the treatment of anaemia associated with chronic kidney disease and end-stage renal disease (ESRD). This broad collaboration focuses on the US, China and all major markets excluding Japan, Europe, the CIS, the Middle East and South Africa, which are covered by an existing agreement between FibroGen and Astellas. Under the arrangement, we agreed to pay FibroGen upfront and subsequent non-contingent payments totalling $350 million, as well as potential development-related milestone payments of up to $465 million, and potential future sales-related milestone payments, in addition to tiered royalty payments on future sales of roxadustat in the low 20% range. Additional development milestones will be payable for any subsequent indications which the companies choose to pursue. We will be responsible for the US commercialisation of roxadustat, with FibroGen undertaking specified promotional activities in the ESRD segment in this market. The companies will also co-commercialise roxadustat in China where FibroGen will be responsible for clinical trials, regulatory matters, manufacturing and medical affairs, and we will oversee promotional activities and commercial distribution.

> In March 2013, we signed an exclusive agreement with Moderna to discover, develop and commercialise pioneering medicines based on *messenger RNA Therapeutics* for the treatment of serious cardiovascular, metabolic and renal diseases, as well as cancer. Under the terms of the agreement, we made an upfront payment of $240 million. We will have exclusive access to select any target of our choice in cardiometabolic and renal diseases, as well as selected targets in oncology, over a period of up to five years for subsequent development of *messenger RNA Therapeutics*. In addition, Moderna is entitled to an additional $180 million for the achievement of three technical milestones. Through this agreement, we have the option to select up to 40 drug products for clinical development and Moderna will be entitled to development and commercial milestone payments as well as royalties on drug sales. We will lead the pre-clinical, clinical development and commercialisation of therapeutics resulting from the agreement and Moderna will be responsible for designing and manufacturing the *messenger RNA Therapeutics* against selected targets. We are currently progressing 19 projects across CVRM and Oncology. Utilising both companies' expertise, significant progress has also been made with the technology platform, with the focus on formulation, safety, and drug metabolism and pharmacokinetics.

We determine the above business development transactions to be significant using a range of factors. We look at the specific circumstances of the individual arrangement and apply several quantitative and qualitative criteria. Because we consider business development transactions to be an extension of our R&D strategy, the expected total value of development payments under the transaction and its proportion of our annual R&D spend, both of which are proxies for overall R&D effort and cost, are important elements of the determination of the significance. Other quantitative criteria we apply include, without limitation, expected levels of future sales, the possible value of milestone payments and the resources used for commercialisation activities (for example, the number of staff). Qualitative factors we consider include, without limitation, new market developments, new territories, new areas of research and strategic implications.

Capitalisation and shareholder return

Capitalisation

The total number of shares in issue at 31 December 2018 was 1,267 million (2017: 1,266 million). 0.8 million Ordinary Shares were issued upon share option exercises for a total of $34 million. Shareholders' equity decreased by $2,492 million to $12,468 million at the year end. Non-controlling interests were $1,576 million (2017: $1,682 million), with the decrease in the year as a result of the losses attributable to shareholders of the non-controlling interest in Acerta Pharma.

Dividend and share repurchases

The Board has recommended a second interim dividend of $1.90 (146.8 pence, 17.46 SEK) to be paid on 27 March 2019. This brings the full-year dividend to $2.80 (215.2 pence, 25.38 SEK). Against Core earnings per share the Group had a dividend cover ratio of 1.2:1 in 2018 (2017: 1.5:1).

This dividend is consistent with the progressive dividend policy, by which the Board intends to maintain or grow the dividend each year.

The Board regularly reviews its distribution policy and its overall financial strategy to continue to strike a balance between the interests of the business, our financial creditors and our shareholders. Having regard for business investment, funding the progressive dividend policy and meeting our debt service obligations, the Board currently believes it is appropriate to continue the suspension of the share repurchase programme which was announced in 2012.

Dividends for 2018

	$	Pence	SEK	Payment date
First interim dividend	0.90	68.4	7.92	10 September 2018
Second interim dividend	1.90	146.8	17.46	27 March 2019
Total	2.80	215.2	25.38	

The Board reviews the level of distributable reserves of the parent company annually and aims to maintain distributable reserves that provide adequate cover for dividend payments. Subject to the filing of these Financial Statements with the UK Companies House, the distributable reserves of the parent company as at 31 December 2018 amounts to $13,443 million (2017: $16,715 million), details are included in the Consolidated Statement of Changes in Equity on page 151. The distributable reserves are sufficient to pay dividends for a number of years, as, when required, the parent company can receive dividends from its subsidiaries to increase distributable reserves.

Future prospects

As outlined earlier in this Annual Report, our strategy is focused on innovation, returning to growth and building a sustainable, durable and more profitable business.

In support of this, we made certain choices around our three strategic priorities:

> Our immediate priorities are to continue to drive Product Sales of our on-market medicines through investment in our Growth Platforms and our portfolio of legacy medicines outside of the Growth Platforms. The Growth Platforms include products in our three main therapy areas, and a focus on the Emerging Markets and Japan. We are also pursuing business development and investment in R&D. We have already accelerated a number of projects and progressed them into Phase III development.
> Our late-stage pipeline is progressing ahead of plans. Our science-driven, collaborative culture is driving increased R&D productivity.
> Our long-term aspiration, in line with our strategic ambition, is to achieve scientific leadership and sustainable growth.

Full Year 2019: additional commentary

In 2019, the sum of Externalisation Revenue and Core other operating income and expense is anticipated to decline versus 2018. Core operating expenses are expected to increase by a low single-digit percentage. Specific support for medicine launches and China sales delivered compelling results in 2018 and elements of that support will continue. The Group will retain flexibility in its investment approach. Core operating profit is anticipated to increase, ahead of Product Sales, by a mid-teens percentage compared with 2018. Without the impact of the reduction in initial income from externalisation and divestment transactions completed in 2018 and 2019, Core operating profit in 2019 is expected to increase at a significantly higher rate, reflecting strong expected growth of the Group's underlying business. Capital expenditure is expected to be broadly stable and restructuring expenses are targeted to reduce compared with 2018. A Core tax rate of 18% to 22% is expected for 2019.

These targets represent management's current estimates and are subject to change. Please see the Cautionary statement regarding forward-looking statements on page 244.

Financial risk management

Financial risk management policies

Insurance

Our risk management processes are described in Risk Overview from page 70. These processes enable us to identify risks that can be partly or entirely mitigated through the use of insurance. We negotiate the best available premium rates with insurance providers on the basis of our extensive risk management procedures. We focus our insurance resources on the most critical areas, or where there is a legal requirement, and where we can get best value for money. We purchase an external multi-line insurance programme to mitigate against significant financial loss arising from business risks including liability, business interruption, property damage, and directors' and officers' liability. In order to contain insurance costs, as of February 2006, we adjusted our product liability coverage profile, accepting uninsured exposure above $100 million.

Taxation

Our approach to managing tax risk is integrated with our broader business risk management and compliance framework. Our approach is to manage tax risks and tax costs in a manner consistent with applicable regulatory requirements and with shareholders' best long-term interests, taking into account operational, economic and reputational factors. We manage tax risks in the context of substantive business transactions.

Treasury

The principal financial risks to which we are exposed are those arising from liquidity, interest rate, foreign currency and credit. We have a centralised treasury function to manage these risks in accordance with Board-approved policies. Specifically, liquidity risk is managed through maintaining access

to a number of sources of funding to meet anticipated funding requirements, including committed bank facilities, cash resources and use of debt factoring.

Interest rate risk is managed through maintaining a debt portfolio that is weighted towards fixed rates of interest. Accordingly, our net interest charge is not significantly affected by movements in floating rates of interest. We monitor the impact of currency on a portfolio basis (to recognise correlation effect), and may hedge to protect against significant adverse impacts on cash flow over the short to medium term. We hedge the currency exposure that arises between the booking and settlement dates on non-local currency purchases and sales by subsidiaries and the external dividend. Significant intra-group loans that give rise to foreign exchange movements are also hedged.

Credit risk is managed through setting and monitoring credit limits appropriate for the assessed risk of the counterparty.

The Group utilises factoring arrangements for selected trade receivables. These factoring arrangements qualify for full derecognition of the associated trade receivables under IFRS 9 'Financial Instruments'.

Our capital and risk management objectives and policies are described in further detail in Note 27 to the Financial Statements from page 187 and in Risk Overview from page 70. Sensitivity analysis of the Group's exposure to exchange rate and interest rate movements is also detailed in Note 27 to the Financial Statements from page 189.

Critical accounting policies and estimates

Our Financial Statements are prepared in accordance with IFRS as adopted by the EU (adopted IFRS) and as issued by the IASB, and the accounting policies employed are set out in the Group Accounting Policies section in the Financial Statements from page 153. In applying these policies, we make estimates and assumptions that affect the Reported amounts of assets and liabilities and disclosure of contingent assets and liabilities. The actual outcome could differ from those estimates. Some of these policies require a high level of judgement because the areas are especially subjective or complex. We believe that the most critical accounting policies and significant areas of judgement and estimation are in:

> revenue recognition
> research and development (including impairment reviews of associated intangible assets)
> business combinations and goodwill (and contingent consideration arising from business combinations)
> litigation and environmental liabilities
> employee benefits
> taxation.

Revenue recognition

Product Sales are recorded at the invoiced amount (excluding inter-company sales and value-added taxes) less movements in estimated accruals for rebates and chargebacks given to managed-care and other customers and product returns, which are a particular feature in the US and are considered to be key estimates. It is the Group's policy to offer a credit note for all returns and to destroy all returned stock in all markets. Cash discounts for prompt payment are also deducted from sales. Sales are recognised when the control of the goods has been transferred to a third party, which is usually when title passes to the customer, either on shipment or on receipt of goods by the customer depending on local trading terms.

Rebates, chargebacks and returns in the US

When invoicing Product Sales in the US, we estimate the rebates and chargebacks that we expect to pay, which are considered to be estimates. These rebates typically arise from sales contracts with third-party managed-care organisations, hospitals, long-term care facilities, group purchasing organisations and various federal or state programmes (Medicaid contracts, supplemental rebates, etc). They can be classified as follows:

> Chargebacks, where we enter into arrangements under which certain parties, typically hospitals, long-term care facilities, group purchasing organisations, the Department of Veterans Affairs, Public Health Service Covered Entities and the Department of Defense, are able to buy products from wholesalers at the lower prices we have contracted with them. The chargeback is the difference between the price we invoice to the wholesaler and the contracted price charged by the wholesaler to the other party. Chargebacks are credited directly to the wholesalers.
> Regulatory, including Medicaid and other federal and state programmes, where we pay rebates based on the specific terms of agreements with the US Department of Health and Human Services and with individual states, which include product usage and information on best prices and average market prices benchmarks.
> Contractual, under which entities such as third-party managed-care organisations are entitled to rebates depending on specified performance provisions, which vary from contract to contract.

The effects of these deductions on our US pharmaceuticals revenue and the movements on US pharmaceuticals revenue provisions are set out overleaf.

Accrual assumptions are built up on a product-by-product and customer-by-customer basis, taking into account specific contract provisions coupled with expected performance, and are then aggregated into a weighted average rebate accrual rate for each of our products. Accrual rates are reviewed and adjusted on an as needed basis. There may be further adjustments when actual rebates are invoiced based on utilisation information submitted to us (in the case of contractual rebates) and claims/invoices are received (in the case of regulatory rebates and chargebacks). We believe that we have made reasonable estimates for future rebates using a similar methodology to that of previous years. Inevitably, however, such estimates involve judgements on aggregate future sales levels, segment mix and the customers' contractual performance.

Overall adjustments between gross and net US Product Sales amounted to $9,662 million in 2018 (2017: $8,468 million) with the increase driven by an overall increase in our US Product Sales and changes in product mix.

Cash discounts are offered to customers to encourage prompt payment. Accruals are calculated based on historical experience and are adjusted to reflect actual experience. Our revenue recognition policy is described within Group accounting policies from page 154.

Industry practice in the US allows wholesalers and pharmacies to return unused stocks within six months of, and up to 12 months after, shelf-life expiry. The customer is credited for the returned product by the issuance of a credit note. Returned products are not exchanged for products from inventory and once a return claim has been determined to be valid and a credit note has been issued to the customer, the returned products are destroyed. At the point of sale in the US, we estimate the quantity and value of products which may ultimately be returned. Our returns accruals in the US are based on actual experience. Our estimate is based on the historical sales and returns information for established products together with market-related information, such as estimated shelf life, product recalls, and estimated stock levels at wholesalers, which we receive via third-party information services. For newly launched products, we use rates based on our experience with similar products or a pre-determined percentage.

Gross to net Product Sales
US pharmaceuticals

	2018 $m	2017 $m	2016 $m
Gross Product Sales	**16,538**	14,637	19,640
Chargebacks	**(2,224)**	(2,299)	(3,449)
Regulatory – Medicaid and state programmes	**(1,304)**	(1,462)	(1,903)
Contractual – Managed-care and Medicare	**(4,600)**	(3,598)	(5,219)
Cash and other discounts	**(286)**	(30)	(358)
Customer returns	**(119)**	(37)	(130)
US Branded Pharmaceutical Fee	**(140)**	3	(145)
Other	**(989)**	(1,045)	(1,071)
Net Product Sales	**6,876**	6,169	7,365

Movement in provisions
US pharmaceuticals

	Brought forward at 1 January 2018 $m	Provision for current year $m	Adjustment in respect of prior years $m	Returns and payments $m	Carried forward at 31 December 2018 $m
Chargebacks	**206**	**2,220**	**4**	**(2,159)**	**271**
Regulatory – Medicaid and state programmes	**749**	**1,482**	**(178)**	**(1,161)**	**892**
Contractual – Managed-care and Medicare	**1,267**	**4,685**	**(85)**	**(4,325)**	**1,542**
Cash and other discounts	**4**	**286**	**–**	**(286)**	**4**
Customer returns	**386**	**119**	**–**	**(144)**	**361**
US Branded Pharmaceutical Fee	**63**	**99**	**41**	**(151)**	**52**
Other	**151**	**989**	**–**	**(996)**	**144**
Total	**2,826**	**9,880**	**(218)**	**(9,222)**	**3,266**

	Brought forward at 1 January 2017 $m	Provision for current year $m	Adjustment in respect of prior years $m	Returns and payments $m	Carried forward at 31 December 2017 $m
Chargebacks	562	2,432	(133)	(2,655)	206
Regulatory – Medicaid and state programmes	807	1,568	(106)	(1,520)	749
Contractual – Managed-care and Medicare	1,443	3,815	(217)	(3,774)	1,267
Cash and other discounts	6	29	1	(32)	4
Customer returns	473	36	1	(124)	386
US Branded Pharmaceutical Fee	260	105	(108)	(194)	63
Other	161	1,030	15	(1,055)	151
Total	3,712	9,015	(547)	(9,354)	2,826

	Brought forward at 1 January 2016 $m	Provision for current year $m	Adjustment in respect of prior years $m	Returns and payments $m	Carried forward at 31 December 2016 $m
Chargebacks	324	3,470	(21)	(3,211)	562
Regulatory – Medicaid and state programmes	777	1,976	(73)	(1,873)	807
Contractual – Managed-care and Medicare	2,206	5,517	(298)	(5,982)	1,443
Cash and other discounts	44	358	–	(396)	6
Customer returns	467	130	–	(124)	473
US Branded Pharmaceutical Fee	264	195	(50)	(149)	260
Other	186	1,071	–	(1,096)	161
Total	4,268	12,717	(442)	(12,831)	3,712

For products facing generic competition, we may lose the ability to estimate the levels of returns from wholesalers with the same degree of precision that we can for products still subject to patent protection. This is because we may have limited or no insight into a number of areas: the actual timing of the generic launch (for example, a generic manufacturer may or may not have produced adequate pre-launch inventory); the pricing and marketing strategy of the competitor; the take-up of the generic; and (in cases where a generic manufacturer has approval to launch only one dose size in a market of several dose sizes) the likely level of switching from one dose to another. Under our accounting policy, revenue is recognised only when the amount of the revenue is considered highly probable not to reverse. Our approach in meeting this condition for products facing generic competition will vary from product to product depending on the specific circumstances.

The adjustment in respect of prior years increased 2018 net US pharmaceuticals revenue by 3.2% (2017: 8.9%; 2016: 6.0%). However, taking into account the adjustments affecting both the current and the prior year, 2017 revenue would have been reduced by 4.5% and 2016 revenue would have been increased by 1.4%, by adjustments between years.

We have distribution service agreements with major wholesaler buyers which serve to reduce the speculative purchasing behaviour of the wholesalers and reduce short-term fluctuations in the level of inventory they hold. We do not offer any incentives to encourage wholesaler speculative buying and attempt, where possible, to restrict shipments to underlying demand when such speculation occurs.

Component revenue accounting

A consequence of charging all internal R&D expenditure to the income statement in the year in which it is incurred (which is normal practice in the pharmaceutical industry) is that we own valuable intangible assets which are not recorded on the Statement of Financial Position. We also own acquired intangible assets which are included on the Statement of Financial Position. As detailed on page 8, our business model means that, from time to time, we sell such assets and generate income. Sales of product lines are often accompanied by an agreement on our part to continue manufacturing the relevant product for a reasonable period (often about two years) while the purchaser constructs its own manufacturing facilities. Details of the Externalisation Revenue accounting and the key judgements involved are described within our Externalisation Revenue accounting policy on page 155.

Research and development (including impairment reviews of associated intangible assets)

Impairment reviews have been carried out on all intangible assets that are in development (and not being amortised), all major intangible assets acquired during the year and all intangible assets that have had indications of impairment during the year. Recoverable amount is determined as the higher of value in use or fair value less costs to sell using a discounted cash flow calculation, where the products' expected cash flows are risk-adjusted over their estimated remaining useful economic life. The determination of the recoverable amounts include key estimates which are highly sensitive and depend upon key assumptions as detailed in Note 9 to the Financial Statements from page 169. Sales forecasts and specific allocated costs (which have both been subject to appropriate senior management sign-off) are risk-adjusted and discounted using appropriate rates based on our post-tax weighted average cost of capital. Our weighted average cost of capital reflects factors such as our capital structure and our costs of debt and equity.

The accounting for our intangible assets is fully explained in Note 9 to the Financial Statements from page 169, including details of the estimates and assumptions we make in impairment testing of intangible assets.

Business combinations and goodwill (and contingent consideration arising from business combinations)

Our business model includes investment in targeted business developments to strengthen our portfolio, pipeline and capabilities. These business development transactions include collaborations, asset in-licences and business acquisitions.

Each transaction is considered to establish whether it qualifies as a business combination by applying the criteria assessment detailed in IFRS 3 'Business Combinations'.

On the acquisition of a business, fair values are attributed to the identifiable assets and liabilities and contingent liabilities unless the fair value cannot be measured reliably, in which case the value is subsumed into goodwill. Attributing fair values is a key judgement. Goodwill is the difference between the fair value of the consideration and the fair value of net assets acquired. Fair value is the price that would be received to sell an asset or pay for a liability in an orderly transaction at the date of acquisition. The price may be directly observable but, in most cases, is estimated using valuation techniques which normally involve predicting future cash flows and applying a market participant discount rate. Further details of our recent business acquisitions are included in Note 26 to the Financial Statements from page 186.

Future contingent elements of consideration, which may include development and launch milestones, revenue threshold milestones and revenue-based royalties, are fair valued at the date of acquisition using decision-tree analysis with key inputs including probability of success, consideration of potential delays and revenue projections based on the Group's internal forecasts. Unsettled amounts of consideration are held at fair value within payables with changes in fair value recognised immediately in profit. Several of our business combinations have included significant amounts of contingent consideration. Details of the movements in the fair value of the contingent consideration in the year, and the range of possible contingent consideration amounts that may eventually become payable are contained in Note 19 to the Financial Statements from page 177.

Where not all the equity of a subsidiary is acquired, the non-controlling interest is recognised either at fair value or at the non-controlling interest's proportionate share of the net assets of the subsidiary, on a case-by-case basis. Put options over non-controlling interests are recognised as a financial liability measured at amortised cost, with a corresponding entry in either retained earnings or against non-controlling interest reserves on a case-by-case basis.

As detailed above, we have significant investments in goodwill and intangible assets as a result of acquisitions of businesses and purchases of assets, such as product development and marketing rights.

Details of the estimates and assumptions we make in our annual impairment testing of goodwill are included in Note 8 to the Financial Statements on page 168. The Group, including acquisitions, is considered a single operating segment for impairment purposes. No impairment of goodwill was identified. A significant portion of our investments in intangible assets and goodwill arose from the restructuring of the joint venture with MSD which commenced in 1998, the acquisition of MedImmune in 2007 and our 2014 acquisition of BMS's interest in the Group's Diabetes Alliance. In addition, our recent business combinations, as detailed in Note 26 to the Financial Statements from page 186, have added significant product, marketing and distribution intangible rights to our intangible asset portfolio. We are satisfied that the carrying values of our intangible assets as at 31 December 2018 are fully justified by estimated future cash flows. The accounting for our intangible assets is fully explained in Note 9 to the Financial Statements from page 169, including details of the estimates and assumptions we make in impairment testing of intangible assets.

Litigation and environmental liabilities

In the normal course of business, contingent liabilities may arise from product-specific and general legal proceedings, from guarantees or from environmental liabilities connected with our current or former sites. Where we believe that potential liabilities have a less than 50% probability of crystallising, or where we are unable to make a reasonable estimate of the liability, we treat them as contingent liabilities. These are not provided for, but are disclosed in Note 29 to the Financial Statements from page 194.

In cases that have been settled or adjudicated, or where quantifiable fines and penalties have been assessed and which are not subject to appeal (or other similar forms of relief), or where a loss is probable (more than 50% assessed probability) and we are able to make a reasonable estimate of the loss, we indicate the loss absorbed or the amount of the provision accrued.

Where it is considered that the Group is more likely than not to prevail, or in the rare circumstances where the amount of the legal liability cannot be estimated reliably, legal costs involved in defending the claim are charged to profit as they are incurred. Where it is considered that we have a valid contract which provides the right to reimbursement (from insurance or otherwise) of legal costs and/or all or part of any loss incurred or for which a provision has been established and we consider recovery to be virtually certain, then the best estimate of the amount expected to be received is recognised as an asset.

Assessments as to whether or not to recognise provisions or assets and of the amounts concerned usually involve a series of complex judgements about future events and can rely heavily on estimates and assumptions. We believe that the provisions recorded are adequate based on currently available information and that the insurance recoveries recorded will be received.

However, given the inherent uncertainties involved in assessing the outcomes of these cases and in estimating the amount of the potential losses and the associated insurance recoveries, we could in future periods incur judgments or insurance settlements that could have a material adverse effect on our results in any particular period.

The position could change over time, and there can, therefore, be no assurance that any losses that result from the outcome of any legal proceedings will not exceed the amount of the provisions that have been booked in the accounts.

Although there can be no assurance regarding the outcome of legal proceedings, we do not currently expect them to have a material adverse effect on our financial position, but they could significantly affect our financial results in any particular period.

Employee benefits

In relation to the Group's defined benefit pension and healthcare arrangements, we apply IAS 19 'Employee Benefits' and recognise all actuarial gains and losses immediately through other comprehensive income. In respect of defined benefit plans, obligations are measured at discounted present value while plan assets are measured at fair value. Given the extent of the assumptions used to determine the values, these are considered to be key estimates.

Investment decisions in respect of defined benefit schemes are based on underlying actuarial and economic circumstances with the intention of ensuring that the schemes have sufficient assets to meet liabilities as they fall due, rather than meeting accounting requirements. The local fiduciary bodies which govern the investment of pension fund assets will invest across a broad range of asset classes and employ specialist investment managers with different investment styles. This will ensure that the investment strategy is diversified across a broad range of return drivers. In addition, local fiduciary bodies will also seek to hedge liability risks (interest rate and inflation risk where applicable) inherent in the measurement of the liabilities and therefore reduce volatility in the funding level, where this is practical and cost effective to do so. The Group plays an active role in providing input and support into these decisions.

In assessing the discount rate applied to the obligations, we have used rates on AA corporate bonds with durations corresponding to the maturities of those obligations, except in Sweden where we have used rates on mortgage bonds as the market in high quality corporate bonds is insufficiently deep. In all cases, the pension costs recorded in the Financial Statements are assessed in accordance with the advice of independent qualified actuaries but require the exercise of significant judgement in relation to assumptions for long-term mortality, price inflation, and future salary and pension increases.

Further details of the estimates and assumptions we make in calculating post-retirement benefit plans are included in Note 21 to the Financial Statements from page 178.

Taxation

Accruals for tax contingencies require management to make judgements and estimates of exposures in relation to tax audit issues. Tax benefits are not recognised unless the tax positions will probably be sustained based upon management's interpretation of applicable laws and regulations and the likelihood of settlement. Once considered probable of not being sustained, management reviews each material tax benefit to assess whether a provision should be taken against full recognition of the benefit on the basis of potential settlement through negotiation and/or litigation. Accruals for tax contingencies are measured using the single best estimate of likely outcome approach.

We face a number of audits in jurisdictions around the world and, in some cases, are in dispute with the tax authorities. The issues under discussion are often complex and can require many years to resolve.

Further details of the estimates and assumptions we make in determining our recorded liability for transfer pricing contingencies and other tax contingencies are included in the Tax section of Note 29 to the Financial Statements from page 194.

Sarbanes-Oxley Act Section 404

As a consequence of our NYSE listing, we are required to comply with those provisions of the Sarbanes-Oxley Act applicable to foreign issuers. Section 404 of the Sarbanes-Oxley Act requires companies annually to assess and make public statements about the quality and effectiveness of their internal control over financial reporting. As regards Sarbanes-Oxley Act Section 404, our approach is based on the Committee of Sponsoring Organizations (COSO) 2013 framework.

Our approach to the assessment has been to select key transaction and financial reporting processes in our largest operating units and a number of specialist areas (eg financial consolidation and reporting, treasury operations and taxation etc), so that, in aggregate, we have covered a significant proportion of the key lines in our Financial Statements. Each of these operating units and specialist areas has ensured that its relevant processes and controls are documented to appropriate standards, taking into account, in particular, the guidance provided by the SEC. We have also reviewed the structure and operation of our 'entity level' control environment. This refers to the overarching control environment, including structure of reviews, checks and balances that are essential to the management of a well-controlled business.

Strategic Report

The following sections make up the Strategic Report, which has been prepared in accordance with the requirements of the Companies Act 2006:

> AstraZeneca at a glance
> Chairman's Statement
> Chief Executive Officer's Review
> Business model and life-cycle of a medicine
> Marketplace
> Strategy
> Key Performance Indicators
> Business Review
> Therapy Area Review
> Risk Overview
> Financial Review

and has been approved and signed on behalf of the Board.

A C N Kemp
Company Secretary
14 February 2019