AstraZeneca

What science can do

AstraZeneca Annual Report and Form 20-F Information 2018

Additional Information

Development Pipeline as at 31 December 2018

AstraZeneca-sponsored or -directed trials

New Molecular Entities (NMEs) and significant indications

Regulatory submission dates shown for assets in Phase III and beyond. As disclosure of compound information is balanced by the business need to maintain confidentiality, information in relation to some compounds listed here has not been disclosed at this time.

Phase I

Compound	Mechanism	Area Under Investigation
Oncology		
AZD0156	ATM inhibitor	solid tumours
AZD1390	ATM inhibitor	glioblastoma
AZD4573	CDK9 inhibitor	haematological malignancies
AZD4785	KRAS inhibitor	solid tumours
AZD5153	BRD4 inhibitor	solid tumours
AZD5991	MCL1 inhibitor	haematological malignancies
AZD9496	selective oestrogen receptor degrader	oestrogen receptor +ve breast cancer
Calquence + AZD6738	BTK inhibitor + ATR inhibitor	haematological malignancies
Calquence + danvatirsen	BTK inhibitor + STAT3 inhibitor	haematological malignancies
Imfinzi + adavosertib	PD-L1 mAb + Wee1 inhibitor	solid tumours
Imfinzi + azacitidine	PD-L1 mAb + azacitidine	myelodysplastic syndrome
Imfinzi + dabrafenib + trametinib	PD-L1 mAb + BRAF inhibitor + MEK inhibitor	melanoma
Imfinzi + *Iressa*	PD-L1 mAb + EGFR inhibitor	non-small cell lung cancer (NSCLC)
Imfinzi + RT (platform) (CLOVER)	PD-L1 mAb + RT	locally-advanced head and neck squamous cell carcinoma, NSCLC, small cell lung cancer
Imfinzi + selumetinib	PD-L1 + MEK inhibitor	solid tumours
Imfinzi + tremelimumab	PD-L1 mAb + CTLA-4 mAb	solid tumours
Imfinzi + tremelimumab + chemotherapy	PD-L1 mAb + CTLA-4 mAb + chemotherapy	1st line pancreatic ductal adenocarcinoma, oesophageal and small cell lung cancer
MEDI2228	BCMA antibody drug conjugate	multiple myeloma
MEDI3726	PSMA antibody drug conjugate	prostate cancer
MEDI5083	CD40 ligand fusion protein	solid tumours
MEDI5752	PD-1/CTLA-4 bispecific mAb	solid tumours
MEDI7247	ASCT2 antibody drug conjugate	haematological malignancies
oleclumab	CD73 mAb	solid tumours
oleclumab + AZD4635	CD73 mAb + A2aR inhibitor	EGFRm NSCLC
oleclumab + *Tagrisso*	CD73 mAb + EGFR inhibitor	EGFRm NSCLC
CVRM		
AZD9977	MCR	CV disease
AZD8233	hypercholesterolaemia	CV disease
MEDI6570	LOX-1 mAb	CV disease
MEDI7219	anti-diabetic	type-2 diabetes
Respiratory		
AZD0449	inhaled JAK inhibitor	asthma
AZD1402	inhaled IL-4Ra	asthma
AZD5634	inhaled ENaC	cystic fibrosis
AZD8154	inhaled PI3Kgd	asthma
MEDI3506	IL-33 mAb	chronic obstructive pulmonary disease (COPD)
Other		
AZD0284	RORg	psoriasis/respiratory
MEDI0700	BAFF/B7RP1 bispecific mAb	systemic lupus erythematosus
MEDI1341	alpha synuclein mAb	Parkinson's disease
MEDI1814	amyloid beta mAb	Alzheimer's disease

Phase II

Compound	Mechanism	Area Under Investigation
Oncology		
adavosertib + chemotherapy	Wee1 inhibitor + chemotherapy	ovarian cancer
AZD2811	Aurora B inhibitor	solid tumours
AZD4547	FGFR inhibitor	solid tumours
AZD4635	A2aR inhibitor	solid tumours
AZD6738	ATR inhibitor	solid tumours
AZD8186	PI3K inhibitor	solid tumours
capivasertib	AKT inhibitor	breast cancer
Imfinzi + AZD5069 or *Imfinzi* + danvatirsen	PD-L1 mAb + CXCR2 antagonist or PD-L1 mAb + STAT3 inhibitor	head and neck squamous cell carcinoma, bladder and NSCLC
Imfinzi + *Lynparza* (BAYOU)	PD-L1 mAb + PARP inhibitor	1st line unresectable stage 4 bladder cancer
Imfinzi + MEDI0457	PD-L1 mAb + DNA HPV vaccine	head and neck squamous cell carcinoma
Imfinzi + MEDI0680	PD-L1 mAb + PD-1 mAb	solid tumours
Imfinzi + monalizumab	PD-L1 mAb + NKG2a mAb	solid tumours
Imfinzi + oleclumab	PD-L1 mAb + CD73 mAb	solid tumours
Imfinzi + tremelimumab	PD-L1 mAb + CTLA-4 mAb	biliary tract, oesophageal
Imfinzi + tremelimumab	PD-L1 mAb + CTLA-4 mAb	gastric cancer
Lynparza + adavosertib	PARP inhibitor + Wee1 inhibitor	solid tumours
Lynparza + AZD6738	PARP inhibitor + ATR inhibitor	gastric cancer
Lynparza + AZD6738 or *Lynparza* + adavosertib (VIOLETTE)	PARP inhibitor + ATR inhibitor or PARP inhibitor + Wee1 inhibitor	breast cancer
Lynparza + *Imfinzi* (MEDIOLA)	PARP inhibitor + PD-L1 mAb	ovarian cancer, breast cancer, gastric cancer and small cell lung cancer
Tagrisso + (selumetinib or savolitinib) (TATTON)	EGFR inhibitor + (MEK inhibitor or MET inhibitor)	advanced EGFRm NSCLC
CVRM		
AZD4831	myeloperoxidase	heart failure with a preserved ejection fraction
AZD5718	FLAP	coronary artery disease
AZD8601	VEGF-A	CV disease
cotadutide (MEDI0382)	GLP-1/glucagon dual agonist	type-2 diabetes/obesity
MEDI5884	cholesterol modulation	CV disease
MEDI6012	LCAT	CV disease
verinurad	URAT1 inhibitor	chronic kidney disease (CKD)
Respiratory		
abediterol	LABA	asthma/COPD
AZD1419	inhaled TLR9 agonist	asthma
AZD7594	inhaled SGRM	asthma/COPD
AZD7986	DPP1	COPD
AZD8871	MABA	COPD
AZD9567	oral SGRM	rheumatoid arthritis/respiratory
PT010	LABA/LAMA/ICS	asthma
tezepelumab	TSLP mAb	atopic dermatitis
Other		
anifrolumab	Type I IFN receptor mAb	lupus nephritis
anifrolumab	Type I IFN receptor mAb	systemic lupus erythematosus (subcutaneous)
MEDI3902	Psl/PcrV bispecific mAb	prevention of nosocomial Pseudomonas aeruginosa pneumonia
MEDI7352	NGF/TNF bispecific mAb	osteoarthritis pain/painful diabetic neuropathy
MEDI8852	influenza A mAb	influenza A treatment
MEDI8897	RSV mAb-YTE	passive RSV prophylaxis
prezalumab	B7RP1 mAb	primary Sjögren's syndrome
suvratoxumab	mAb binding to S. aureus toxin	prevention of nosocomial Staphylococcus aureus pneumonia

Development Pipeline
continued

Phase III/Pivotal Phase II/Registration

Compound	Mechanism	Area Under Investigation	Estimated Filing US	EU	Japan	China
Oncology						
Calquence	BTK inhibitor	relapsed/refractory mantle cell lymphoma	Launched			
Imfinzi + tremelimumab + chemotherapy (POSEIDON)	PD-L1 mAb + CTLA-4 mAb + chemotherapy	1st line NSCLC	H2 2019	H2 2019	H2 2019	2020
Imfinzi + tremelimumab + CRT (ADRIATIC)	PD-L1 mAb + CTLA-4 mAb + CRT	Limited disease small cell lung cancer	2020+	2020+	2020+	2020+
Imfinzi + tremelimumab + SoC (CASPIAN)	PD-L1 mAb + CTLA-4 mAb + SoC	1st line small cell lung cancer	H2 2019	H2 2019	H2 2019	2020
Imfinzi + tremelimumab + SoC (NILE)	PD-L1 mAb + CTLA-4 mAb + SoC	1st line urothelial cancer	2020+	2020+	2020+	
Imfinzi + tremelimumab (DANUBE)	PD-L1 mAb + CTLA-4 mAb	1st line bladder cancer	H2 2019	H2 2019	H2 2019	
Imfinzi + tremelimumab (HIMALAYA)	PD-L1 mAb + CTLA-4 mAb	1st line hepatocellular carcinoma	2020+	2020+	2020+	2020+
Imfinzi + tremelimumab (KESTREL)	PD-L1 mAb + CTLA-4 mAb	1st line head and neck squamous cell carcinoma	H1 2019	H2 2019	H2 2019	
Imfinzi + tremelimumab (NEPTUNE)	PD-L1 mAb + CTLA-4 mAb	1st line NSCLC	H2 2019	H2 2019	H2 2019	2020
Lumoxiti (PLAIT)	anti-CD22 recombinant immunotoxin	3rd line hairy cell leukaemia	Launched (Orphan Drug, Priority Review)	2020		
Lynparza + cediranib (CONCERTO)	PARP inhibitor + VEGF inhibitor	recurrent platinum-resistant ovarian cancer	2020			
savolitinib (SAVOIR)	MET inhibitor	papillary renal cell carcinoma	2020	2020		
selumetinib (SPRINT)	MEK inhibitor	paediatric neurofibromatosis type-1	H2 2019 (Orphan Drug)	H2 2019 (Orphan Drug)		
CVRM						
Epanova	omega-3 carboxylic acids	severe hypertriglyceridaemia	Approved			
Lokelma	potassium binder	hyperkalaemia	Approved	Approved	H2 2019	2020
roxadustat (OLYMPUS, ROCKIES)	hypoxia-inducible factor prolyl hydroxylase inhibitor	anaemia in CKD/end-stage renal disease	H1 2019			Approved
Respiratory						
Bevespi Aerosphere (PT003)	LABA/LAMA	COPD	Launched	Approved	Accepted	Accepted
Fasenra (CALIMA, SIROCCO, ZONDA, BISE, BORA, GREGALE)	IL-5R mAb	severe, uncontrolled asthma	Launched	Launched	Launched	2020+
PT010	LABA/LAMA/ICS	COPD	2019	2019	Accepted	Accepted
PT027	ICS/SABA	asthma	2020+			
tezepelumab (NAVIGATOR, SOURCE)	TSLP mAb	severe, uncontrolled asthma	2020+	2020+	2020+	
Other						
anifrolumab (TULIP)	Type I IFN receptor mAb	systemic lupus erythematosus	2020 (Fast Track designation)	2020	2020	

Significant Life-cycle Management

Compound	Mechanism	Area Under Investigation	Estimated Filing US	EU	Japan	China
Oncology						
Calquence	BTK inhibitor	1st line chronic lymphocytic leukaemia	2020 (Orphan Drug)	2020 (Orphan Drug)		2020+
Calquence	BTK inhibitor	relapsed/refractory chronic lymphocytic leukaemia	2020 (Orphan Drug)	2020 (Orphan Drug)		
Calquence	BTK inhibitor	relapsed/refractory chronic lymphocytic leukaemia, high risk	H2 2019 (Orphan Drug)	H2 2019 (Orphan Drug)		
Calquence	BTK inhibitor	haematological malignancies				
Calquence	BTK inhibitor	1st line mantle cell lymphoma	2020+ (Orphan Drug)	2020+		2020+
Imfinzi	PD-L1 mAb	solid tumours				
Imfinzi (PEARL, China)	PD-L1 mAb	1st line NSCLC	N/A	N/A	N/A	2020
Imfinzi (PACIFIC)	PD-L1 mAb	locally advanced (stage 3) NSCLC	Approved (Breakthrough designation, Priority Review)	Approved	Approved	Accepted
Imfinzi (POTOMAC)	PD-L1 mAb	non-muscle invasive bladder cancer	N/A	2020+	2020+	N/A
Imfinzi + CRT (PACIFIC-2)	PD-L1 mAb + CRT	locally-advanced (stage 3) NSCLC	2020+	2020+	2020+	
Imfinzi + CRT (PACIFIC-5, China)	PD-L1 mAb + CRT	locally-advanced (stage 3) NSCLC	N/A	N/A	N/A	2020+
Imfinzi + CTx neoadjuvant (AEGEAN)	PD-L1 mAb + CTx	locally-advanced (stage 3) NSCLC	2020+	2020+	2020+	
Imfinzi + CTx (NIAGARA)	PD-L1 mAb + CTx	muscle invasive bladder cancer	2020+	2020+	2020+	
Imfinzi + VEGF + TACE (EMERALD-1)	PD-L1 mAb + VEGF + TACE	locoregional hepatocellar carcinoma	2020+	2020+	2020+	2020+
Lynparza (OlympiA)	PARP inhibitor	gBRCA adjuvant breast cancer	2020+	2020+	2020+	
Lynparza (OlympiAD)	PARP inhibitor	gBRCA metastatic breast cancer	Launched (Priority Review)	Accepted	Approved (Orphan Drug, Priority Review)	H1 2019
Lynparza (POLO)	PARP inhibitor	pancreatic cancer	H2 2019 (Orphan Drug)	H2 2019		
Lynparza (SOLO-3)	PARP inhibitor	gBRCA PSR ovarian cancer	H2 2019			
Lynparza + abiraterone (PROpel)	PARP inhibitor + NHA	prostate cancer	2020+	2020+	2020+	2020+
Lynparza (PROfound)	PARP inhibitor	prostate cancer	2020 (Breakthrough designation)	2020	2020	2020+
Lynparza (SOLO-1)	PARP inhibitor	1st line BRCAm ovarian cancer	Approved (Priority Review)	Accepted	Accepted	Accepted (Priority Review)
Lynparza (SOLO-2)	PARP inhibitor	2nd line or greater BRCAm PSR ovarian cancer, maintenance monotherapy	Approved (Priority Review)	Approved	Approved (Orphan Drug)	Approved
Tagrisso (LAURA)	EGFR inhibitor	stage 3 EGFRm NSCLC	2020+	2020+	2020+	2020+
Tagrisso (ADAURA)	EGFR inhibitor	adjuvant EGFRm NSCLC	2020+	2020+	2020+	2020+
Tagrisso (FLAURA)	EGFR inhibitor	1st line advanced EGFRm NSCLC	Approved (Breakthrough designation)	Approved	Approved	Accepted

Development Pipeline
continued

Significant Life-cycle Management *continued*

Compound	Mechanism	Area Under Investigation	Estimated Filing US	EU	Japan	China
CVRM						
Brilinta/Brilique (HESTIA)	P2Y12 receptor antagonist	prevention of vaso-occlusive crises in paediatric patients with sickle cell disease	2020+	2020+		
Brilinta/Brilique (THEMIS)	P2Y12 receptor antagonist	CV outcomes trial in patients with coronary artery disease and type-2 diabetes without a previous history of myocardial infarction or stroke	H2 2019	H2 2019	H2 2019	H2 2019
Brilinta/Brilique (THALES)	P2Y12 receptor antagonist	acute ischaemic stroke or transient ischaemic attack	2020	2020		2020
Bydureon (EXSCEL)	GLP-1 receptor agonist	type-2 diabetes outcomes study	Accepted	Approved	N/A	Accepted
Bydureon BCise (autoinjector)	GLP-1 receptor agonist	type-2 diabetes	Launched	Approved		
Epanova (STRENGTH)	omega-3 carboxylic acids	CV outcomes study in statin-treated patients at high CV risk, with persistent hypertriglyceridaemia plus low HDL-cholesterol	2020	2020	2020	2020
Farxiga/Forxiga Dapa-HF	SGLT-2 inhibitor	worsening heart failure or CV death in patients with chronic heart failure (HFrEF)	2020	2020	2020	2020
Farxiga/Forxiga (DELIVER)	SGLT-2 inhibitor	worsening heart failure or CV death in patients with chronic heart failure (HFpEF)	2020+	2020+	2020+	2020+
Farxiga/Forxiga Dapa-CKD	SGLT-2 inhibitor	renal outcomes and CV mortality in patients with CKD	2020+	2020+	2020+	2020+
Farxiga/Forxiga (DEPICT)	SGLT-2 inhibitor	type-1 diabetes	Accepted	Accepted	Accepted	
Farxiga/Forxiga (DECLARE)	SGLT-2 inhibitor	CV outcomes trial in patients with type-2 diabetes	H1 2019	H1 2019		H1 2019
Qtern	DPP-4 inhibitor/SGLT-2 inhibitor FDC	type-2 diabetes	Launched	Launched		
roxadustat	hypoxia-inducible factor prolyl hydroxylase inhibitor	anaemia in myelodysplastic syndrome	2020+			2020+
saxagliptin/dapagliflozin metformin	DPP-4 inhibitor/SGLT-2 inhibitor	type-2 diabetes	Accepted	Accepted		
Xigduo XR/*Xigduo*	SGLT-2 inhibitor/ metformin FDC	type-2 diabetes	Launched	Launched		2020
Respiratory						
Duaklir Genuair	LAMA/LABA	COPD	Accepted	Launched		2020
Fasenra (TERRANOVA, GALATHEA)	IL-5R mAb	COPD				
Fasenra (OSTRO)	IL-5R mAb	nasal polyposis	2020	2020		
Symbicort (SYGMA)	ICS/LABA	as-needed use in mild asthma	N/A	Accepted	N/A	H2 2019
Other						
Linzess (linaclotide)	GC-C receptor peptide agonist	irritable bowel syndrome with constipation				Approved
Nexium	proton pump inhibitor	stress ulcer prophylaxis				Accepted

Patent Expiries of Key Marketed Products

Patents covering our products are or may be challenged by third parties. Generic products may be launched 'at risk' and our patents may be revoked, circumvented or found not to be infringed. For more information, please see Risk from page 220. Many of our products are subject to challenges by third parties. Details of material challenges by third parties can be found in Note 29 to the Financial Statements from page 196. The expiry dates shown below include granted SPC/PTE and/or Paediatric Exclusivity periods (as appropriate). In Europe, the exact SPC situation may vary by country as different Patent Offices grant SPCs at different rates. Expiry dates in red relate to new molecular entity patents, the remaining dates relate to other patents. The expiry dates of relevant regulatory data exclusivity periods are not represented in the table below. A number of our products are subject to generic competition in one or more markets.

Key marketed products	Description	US	China	EU[1]	Japan	US Product Sales ($m)			Aggregate Revenue for China, Japan and Europe[2] Product Sales ($m)		
						2018	2017	2016	**2018**	2017	2016
Atacand[3] (candesartan cilexitil)	An angiotensin II antagonist for the 1st line treatment of hypertension and symptomatic heart failure	expired	[4]	expired	[4]	**13**	19	36	**62**	86	97
Bevespi Aerosphere (glycopyrrolate/ formoterol)	A combination of a long-acting muscarinic antagonist (LAMA) and a long-acting beta2-agonist (LABA) used for the long-term maintenance treatment of airflow obstruction in COPD	2030-2031	2030	2030	2030	**33**	16	2	**–**	–	–
Brilinta/ *Brilique* (ticagrelor)	An oral P2Y12 platelet inhibitor for acute coronary syndromes (ACS) (ticagrelor 90mg) or continuation therapy in high-risk patients (ticagrelor 60mg) with a history of myocardial infarction (MI)	2018-2024[5], 2021-2030	2018, 2019[6], 2021[7]	2018-2024, 2021[8]-2027[9]	2023-2024, 2025-2030	**588**	509	348	**532**	402	347
Bydureon/ *Bydureon BCise* (exenatide XR injectable suspension)	A once-weekly injectable glucagon-like peptide-1 (GLP-1) receptor agonist available as a single-dose tray, a single-dose pen or autoinjector device indicated as monotherapy and as part of combination therapy adjunct to diet and exercise to improve glycaemic control in adults with type-2 diabetes	2018-2028, 2030[10]	2020-2028, 2029[10]	2018-2028, 2029[10]	2018-2028, 2029[10]	**475**	458	463	**85**	93	109
Byetta (exenatide injection)	A twice-daily injectable GLP-1 receptor agonist indicated to improve glycaemic control in adults with type-2 diabetes	2018-2020[11]	2020	2018-2021	2018-2020	**74**	114	164	**34**	39	62
Calquence (acalabrutinib)	A selective inhibitor of Bruton's tyrosine kinase indicated for the treatment of mantle cell lymphoma (MCL) and in development for the treatment of multiple B-cell malignancies and other cancers	2026-2032, 2036	2032	2032	2032	**62**	–	–	**–**	–	–
Crestor (rosuvastatin calcium)	A statin for dyslipidaemia and hypercholesterolaemia	2018-2022[12]	2020-2021	2020	2023	**170**	373	1,223	**825**	1,528	1,698
Daliresp/ *Daxas* (roflumilast)	An oral phosphodiesterase-4 inhibitor for adults with severe COPD to decrease their number of exacerbations	2020, 2023-2024	2023	2019[13], 2023		**155**	167	134	**28**	26	15
Duaklir (aclidinium/ formoterol)	A fixed-dose combination of a LAMA and a LABA for the maintenance treatment of COPD	2020, 2025, 2022-2029[14]	2020, 2022-2027	2025, 2022-2029	2025, 2021-2029	**–**	–	–	**91**	77	62
Fasenra (benralizumab)	A monoclonal antibody for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype, which directly targets and depletes eosinophils by recruiting natural killer cells and inducing apoptosis (programmed cell death)	2020, 2028-2034	2021, 2028	2020, 2028	2020	**218**	–	–	**77**	–	–
Faslodex (fulvestrant)	An injectable oestrogen receptor antagonist. Used for the treatment of hormone receptor positive advanced breast cancer that has progressed following treatment with prior endocrine therapy	2021[15]		2021	2026	**537**	492	438	**382**	352	311
Farxiga/ *Forxiga* (dapagliflozin)	A selective inhibitor of human sodium-glucose co-transporter 2 (SGLT-2 inhibitor) indicated as monotherapy, and as part of combination therapy, adjunct to diet and exercise to improve glycaemic control in adult patients with type-2 diabetes	2020, 2025*, 2020-2030	2020-2023, 2028	2020-2027	2024-2025, 2028	**591**	355	358	**394**	245	175
Fluenz Tetra/ *FluMist* Quadrivalent (live attenuated influenza vaccine)	A live attenuated vaccine indicated for active immunisation for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine	2018-2026	2020-2025	2020-2026	2020-2025	**15**	–	33	**91**	76	65

Patent Expiries of Key Marketed Products *continued*

Key marketed products	Description	US	China	EU[1]	Japan	US Product Sales ($m)			Aggregate Revenue for China, Japan and Europe[2] Product Sales ($m)		
						2018	2017	2016	**2018**	2017	2016
Imfinzi (durvalumab)	A human monoclonal antibody that blocks PD-L1 interaction with PD-1 and CD80 on T cells, countering the tumour's immune-evading tactics and inducing an immune response. It is currently indicated for the treatment of locally advanced or metastatic urothelial carcinoma and unresectable stage 3 non-small cell lung cancer (NSCLC)	2030	2030	2030	2030	**564**	19	–	**62**	–	–
Iressa (gefitinib)	An epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) that acts to block signals for cancer cell growth and survival in advanced NSCLC	[16]	2023	2019[17], 2023	2018, 2023	**26**	39	23	**376**	367	358
Komboglyze/ Kombiglyze XR[18] (saxagliptin/ metformin)	Combines saxagliptin and metformin as either *Komboglyze* – a twice-daily tablet for type-2 diabetes, or *Kombiglyze* XR – an extended release once-daily tablet for type-2 diabetes	2023, 2025	2021, 2025	2021-2026, 2025	[19]	**–**	111	145	**–**	–	–
Lokelma (sodium zirconium cyclosilicate)	An insoluble, non-absorbed sodium zirconium silicate, formulated as a powder for oral suspension, that acts as a highly-selective potassium-removing agent for the treatment of hyperkalaemia	2019, 2032-2033, 2035	2033	2032	2032-2033	**–**	–	–	**–**	–	–
Lumoxiti (moxetumomab pasudotox-tdfk)	A CD22-directed cytotoxin and a first-in-class treatment in the US for adult patients with relapsed or refractory hairy cell leukaemia (HCL)	2022-2024, 2031-2032	2031	2022, 2031	2031	**–**	–	–	**–**	–	–
Lynparza (olaparib)	An oral poly ADP-ribose polymerase (PARP) inhibitor that may exploit tumour DNA damage response (DDR) pathway deficiencies to potentially kill cancer cells. It is indicated for the treatment of women with BRCAm ovarian cancer and metastatic breast cancer	2022-2024, 2028*, 2029[20], 2024-2031	2021-2024, 2024-2027, 2029[20], 2024	2021-2029, 2024-2027, 2029[20], 2024	2021-2029, 2024-2027, 2029[20], 2024	**345**	141	127	**250**	130	81
Movantik/ Moventig (naloxegol)	A once-daily, peripherally acting mu-opioid receptor antagonist approved for the treatment of opioid-induced constipation (OIC) in adult patients. The indication varies by jurisdiction	2022-2027, 2028*, 2032	2024, 2031	2022-2024, 2029*[21], 2031	2022-2024, 2031	**108**	120	90	**–**	2	–
Nexium (esomeprazole)	A proton pump inhibitor used to treat acid-related diseases	2018-2020[22]	2018-2019	2018	2018, 2018-2019	**287**	499	526	**955**	973	975
Onglyza (saxagliptin)	An oral dipeptidyl peptidase 4 (DPP-4) inhibitor for type-2 diabetes	2023, 2028	2021, 2025	2024, 2025	[19]	**109**	209	231	**95**	114	120
Pulmicort (budesonide)	An inhaled corticosteroid for maintenance treatment of asthma	2018-2019[23]	2018[24]	2018[24]	2018[24]	**116**	156	174	**975**	847	732
Qtern (dapagliflozin/ saxagliptin)	A once-daily oral treatment combination of dapagliflozin (10mg) and saxagliptin (5mg) indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type-2 diabetes who have inadequate control with dapagliflozin or who are already treated with dapagliflozin and saxagliptin	2020, 2025*, 2020-2029	2020-2023	2020-2027	2024-2025	**–**	4	–	**5**	–	–
Seloken/ Toprol-XL (metoprolol succinate)	A beta-blocker once-daily tablet for control of hypertension, heart failure and angina	expired	expired	expired	expired	**39**	37	95	**488**	470	462
Seroquel XR (quetiapine)	Generally approved for the treatment of schizophrenia, bipolar disorder, major depressive disorder and, on a more limited basis, for generalised anxiety disorder	expired	expired[25]	expired	[26]	**73**	175	515	**70**	82	134
Symbicort (budesonide/ formoterol)	A combination of an inhaled corticosteroid and a fast onset LABA for maintenance treatment of asthma and COPD either as *Symbicort Turbuhaler* or *Symbicort* pMDI (pressurised metered-dose inhaler)	2019-2029[27]	2018[28]	2018-2019[28]	2019-2020[28]	**862**	1,099	1,242	**1,220**	1,201	1,276

Key marketed products	Description	US	China	EU[1]	Japan	US Product Sales ($m)			Aggregate Revenue for China, Japan and Europe[2] Product Sales ($m)		
						2018	2017	2016	**2018**	2017	2016
Synagis (palivizumab)	A humanised mAb used to prevent serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in paediatric patients at high risk of acquiring RSV disease	2023		2023	2023	**287**	317	325	**377**	370	352
Tagrisso (osimertinib)	An EGFR-TKI indicated for patients with metastatic EGFR T790M mutation-positive NSCLC	2032	2032	2032	2034	**869**	405	254	**808**	486	158
Tudorza/Eklira Genuair (aclidinium)	A LAMA for the maintenance treatment of COPD	2020, 2025, 2022-2029	2020, 2022-2027	2025, 2022-2029	2025, 2021-2029	**25**	66	77	**75**	74	84
Xigduo/Xigduo XR (dapagliflozin/ metformin)	Combines dapagliflozin and metformin as either *Xigduo* – a twice-daily tablet to improve glycaemic control in adult patients with type-2 diabetes who are inadequately controlled on metformin alone or *Xigduo* XR – an extended release once-daily tablet to improve glycaemic control in adult patients with type-2 diabetes who are inadequately controlled on metformin alone	2020, 2025*, 2020-2030	2020-2023	2020-2028	2024-2025, 2030	**114**	134	99	**83**	58	37
Zoladex (goserelin acetate implant)	A luteinising hormone-releasing hormone (LHRH) agonist used to treat prostate cancer, breast cancer and certain benign gynaecological disorders	2022[29]	2021	2021	2021	**8**	15	35	**508**	483	498

* Date represents expiry of a pending SPC/PTE and/or Paediatric Exclusivity period.

1 Expiry in major EU markets.

2 The Product Sales reflected are for Europe Region as defined in Market definitions on page 239.

3 *Atacand HCT* in US.

4 Takeda retained rights.

5 Separate settlements with ANDA challengers for a licensed entry date corresponding to the expiry of US Patent No. RE46,276, subject to regulatory approval.

6 The patent was invalidated during invalidation proceedings at the Chinese Patent Office (CNIPA). In December 2018, however, the Beijing High People's Court vacated the invalidation decision and remanded the case back to the CNIPA for further processing in view of the Court's decision upholding the validity of the patent.

7 The patent was invalidated during invalidation proceedings at the CNIPA. The patentee has appealed that decision.

8 The patent was revoked during opposition proceedings at the European Patent Office (EPO). The patentee has appealed that decision.

9 The patent is the subject of a pending opposition proceeding at the EPO.

10 Patent expiry date relates to *BCise*.

11 Separate settlements with ANDA challengers for a licensed entry date of 15 October 2017, or later, subject to regulatory approval.

12 A settlement agreement in the US permitted Watson Laboratories, Inc. and Actavis, Inc. (together, Watson) to begin selling its generic version of *Crestor* and its rosuvastatin zinc product from 2 May 2016.

13 There is eight years' data exclusivity and two years' market exclusivity for *Daxas* in the EU to 5 July 2020.

14 NDA filed 31 May 2018.

15 Settled with various generic companies for licensed entry dates of 25 March 2019 or later.

16 In the US, *Iressa* has seven years' Orphan Drug exclusivity to 13 July 2022.

17 SPCs expire 2 March 2019. There is eight years' data exclusivity and two years' market exclusivity for *Iressa* in the EU to 24 June 2019.

18 *Komboglyze/Kombiglyze* XR revenue is included in the *Onglyza* revenue figure.

19 AstraZeneca does not have commercialisation rights.

20 Patent expiry date relates to the tablet formulation.

21 ProStrakan Group (a subsidiary of Kyowa Hakko Kirin) is exclusively licensed in the EU, Iceland, Norway, Switzerland and Liechtenstein.

22 Licence agreements have allowed generic companies to launch generic capsule versions in the US.

23 A licence agreement with Teva permits its ongoing sale in the US of a generic version from December 2009. The 2018 expiry relates to the Flexhaler device, while the 2019 expiry relates to the formulation in the Flexhaler presentation and also to *Respules*.

24 The 2018 expiry relates to the formulation in the *Turbuhaler* presentation and to a process useful for the *Respules* product.

25 Rights licensed to Luye Pharma.

26 Rights licensed to Astellas.

27 Patent expiry dates relate to the *Symbicort* pMDI product, including any granted Paediatric Exclusivity term.

28 Patent expiry dates relate to the *Symbicort Turbuhaler* product.

29 Rights licensed to TerSera.

Risks and uncertainties

Operating in the pharmaceutical sector carries various inherent risks and uncertainties that may affect our business. In this section, we describe the risks and uncertainties that we consider material to our business in that they may have a significant effect on our financial condition, results of operations, and/or reputation.

These risks are not listed in any particular order of priority and have been categorised consistently with the Principal Risks detailed from page 72, which are included below along with the other risks that we face. We believe that the forward-looking statements about AstraZeneca in this Annual Report, identified by words such as 'anticipates', 'believes', 'expects' and 'intends', and that include, among other things, Future prospects in the Financial Review on page 86, are based on reasonable assumptions. However, forward-looking statements involve inherent risks and uncertainties such as those summarised below. They relate to events that may occur in the future, that may be influenced by factors beyond our control and that may have actual outcomes materially different from our expectations. Therefore, other risks, unknown or not currently considered material, could have a material adverse effect on our financial condition or results of operations.

Product pipeline and IP risks	Impact
Failure or delay in delivery of pipeline or launch of new products	
Our continued success depends on the development and successful launch of innovative new drugs. The development of pharmaceutical product candidates is a complex, risky and lengthy process involving significant financial, R&D and other resources. A project may fail at any stage of the process due to various factors, including failure to obtain the required regulatory or marketing approvals for the product candidate or for its manufacturing facilities, unfavourable clinical efficacy data, safety concerns, failure to demonstrate adequate cost-effective benefits to regulatory authorities and/or payers and the emergence of competing products. More details of projects that have suffered setbacks or failures during 2018 can be found in the Therapy Area Review. The anticipated launch dates of major new products significantly affect our business, including investment in large clinical studies, the manufacture of pre-launch product stocks, investment in marketing materials pre-launch, sales force training and the timing of anticipated future revenue streams from new Product Sales. Launch dates are primarily driven by our development programmes and the demands from various factors, including adverse findings in pre-clinical or clinical studies, regulatory demands, price negotiation, competitor activity and technology transfer. More complex and stringent regulations govern the manufacturing and supply of biologics products, thus impacting the production and release schedules of such products more significantly. In addition to developing products in-house, we also expand our product portfolio and geographical presence through licensing arrangements and strategic collaborations, which are key to growing and strengthening our business. The success of such arrangements is largely dependent on the technology and other IP rights we acquire or license, and the resources, efforts and skills of our partners. Disputes or difficulties in our relationship with our collaborators or partners may arise, for example, due to conflicting priorities or conflicts of interest between parties. In many cases we make milestone payments well in advance of the commercialisation of the products, with no assurance that we will recoup these payments. We experience strong competition from other pharmaceutical companies in respect of licensing arrangements, strategic collaborations, and acquisition targets.	Failure or delay in development of new product candidates that achieve the expected commercial success could frustrate the achievement of development targets, adversely affect the reputation of our R&D capabilities, and is likely to materially adversely affect our business and results of operations. See also Failure to achieve strategic plans or meet targets and expectations on page 229. Since our business model and strategy rely on the success of relatively few compounds, the failure of any compound in our late-stage pipeline or in-line products may have a significant negative effect on our business or results of operations. Significant delays to anticipated launch dates of new products could have a material adverse effect on our financial position and/or results of operations. For example, for the launch of products that are seasonal in nature, delays in regulatory approvals or manufacturing difficulties may delay launch to the next season which, in turn, may significantly reduce the return on costs incurred in preparing for the launch for that season. Furthermore, in immuno-oncology for example, speed to market is critical given the large number of clinical trials being conducted by other companies. In addition, a delayed launch may lead to increased costs if, for example, marketing and sales efforts need to be rescheduled or performed for longer than expected. Failure to complete collaborative projects in a timely, cost-effective manner may limit our ability to access a greater portfolio of products, IP, technology and shared expertise. Disputes and difficulties with our partners may erode or eliminate the benefits of our alliances and collaborations. In addition, failure to perform on the part of parties to externalisation transactions may diminish the future value of those transactions or, in some cases, allow a competitor to beat us to market with a similar or first-in-class product. Delay of launch can also erode the term of patent exclusivity. Competition from other pharmaceutical companies means that we may be unsuccessful in implementing some of our intended projects or we may have to pay a significant premium over book or market values for our acquisitions.

Product pipeline and IP risks	Impact

Difficulties in obtaining or maintaining regulatory drug approval for products

We are subject to strict controls on the commercialisation processes for our pharmaceutical products, including their development, manufacture, distribution and marketing. The criteria for establishing safety, efficacy and quality, which are essential for securing marketing approvals, vary by country and by region. Regulators can refuse to grant approval or may require additional data before approval is granted or as a post-approval commitment, even though the medicine may already be approved or launched in other countries.

Factors, including advances in science and technology, evolving regulatory science, new laws and policies, and different approaches to benefit/risk tolerance by regulatory authorities, the general public, and other third-party public interest groups are known to influence the approvability of new drugs. While we seek to manage most of these risks, unanticipated and unpredictable policymaking by governments and regulators, limited regulatory authority resources or conflicting priorities often lead to delays in regulatory approvals.

We may be required to generate additional data after a drug's approval because a regulatory authority may have concerns that impact the benefit/risk profile of the drug. For our marketed drugs, new data or meta-analyses have the potential to drive changes in the approval status or labelling. In addition, recent years have seen an increase in post-marketing regulatory requirements and commitments, an increased call for third-party access to regulatory and clinical trial data packages for independent analysis and interpretation, and broader data transparency. Such transparency, while important, could lead to inappropriate or incorrect data analyses which may damage the integrity of our products and our Company's reputation.

Delays in regulatory reviews and approvals could delay our ability to market our products and may adversely affect our revenue. In addition, post-approval requirements, including additional clinical trials, could result in increased costs, and may impact the labelling and approval status of currently marketed products.

With the UK planning to leave the EU by the end of March 2019, intense work is ongoing to manage Brexit related changes, identify scenarios for the many uncertainties still to be resolved, and determine the new UK requirements moving forward. This includes transferring licences and authorisations for EU markets currently held in the UK to an EU member state and building capability to test medicines in the EU for which such testing is currently undertaken in the UK. UK licences also need to be separated out from centrally approved products in the EU. These actions are required to ensure appropriate regulatory requirements can be met both in the EU and UK post 29 March 2019. Based on our corporate planning assumptions for a no deal Brexit, with no transition period, the Company is taking steps to protect product supply both in the UK and EU. Changes in regulatory reviews and approvals, and safety surveillance will certainly have implications on resources, ways of working and costs.

Failure to obtain, defend and enforce effective IP protection and IP challenges by third parties

A pharmaceutical product may be protected from being copied for a limited period of time under certain patent rights and/or related IP rights, such as Regulatory Data Protection or Orphan Drug status. Typically, products protected by such rights generate significantly higher revenues than those not protected. Our ability to obtain, maintain, defend and enforce patents and other IP rights in relation to our products is an important element in protecting and recouping our investment in R&D and creating long-term value for the business. Some countries in which we operate do not offer robust IP protection. This may be because IP laws are still developing, the scope of those laws is limited or the political environment does not support such legislation. We also recognise increasing use of compulsory licensing in some countries in which we operate.

We may also 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 and there can be no guarantee of success for either party in patent proceedings and litigation.

We also bear the risk that our products may be found to infringe patents owned or licensed by third parties, including research-based and generic pharmaceutical companies and individuals. These third parties may seek remedies for patent infringement, including injunctions (for example, preventing the marketing of one of our products) and damages (for example, research-based competitors are alleging infringement of their patents and are seeking damages in relation to our marketing of *Imfinzi* and *Calquence*).

Details of material patent proceedings and litigation matters can be found in Note 29 to the Financial Statements from page 194.

Limitations on the availability of patent protection, the ability to obtain related IP rights or the use of compulsory licensing in certain countries in which we operate, as well as our ability to defend and enforce our patents, could allow for earlier entry of generic or biosimilar competitor products. This could have a material adverse effect on the pricing and sales of our products and, consequently, could materially adversely affect our revenues.

Third parties may be awarded remedies for alleged infringement of their IP, for example injunctions and damages for alleged patent infringement. In the US, courts may order enhanced (ie up to treble) damages for alleged wilful infringement of patents. From time to time we may acquire licences, discontinue activities and/or modify processes to avoid claims of patent infringement. These steps could entail significant costs and our revenue and margins could be materially adversely affected.

More information about protecting our IP, the risk of patent litigation and the early loss of IP rights is contained in the Intellectual Property section on page 35, the Competitive pressures including expiry or loss of IP rights and generic competition risk on page 222 and Note 29 to the Financial Statements from page 194.

Commercialisation risks	Impact

Competitive pressures including expiry or loss of IP rights, and generic competition

A pharmaceutical product competes with other products marketed by research-based pharmaceutical companies and with generic or biosimilar drugs marketed by generic drug manufacturers.

Generic versions of products, including biosimilars, are often sold at lower prices than branded products, as the manufacturer does not have to recoup the significant cost of R&D investment and market development. Expiry or loss of IP rights can materially adversely affect our revenues and financial condition due to the launch of cheaper generic copies of the product in the country where the rights have expired or been lost (see the table in the Patent Expiries of Key Marketed Products section from page 217). For example, in 2018 our US Product Sales of *Crestor* fell to $170 million (2017: $373 million) following the launch of generics.

Additionally, the expiry or loss of patents covering other innovator companies' products may also lead to increased competition and pricing pressure for our own, still-patented products in the same product class due to the availability of lower priced generic products in that product class.

Generic manufacturers may also take advantage of the failure of certain countries to properly enforce Regulatory Data Protection or other related IP rights and may launch generics during this protected period. This is a particular risk in some Emerging Markets where appropriate patent protection or other related IP rights may be difficult to obtain or enforce.

The biosimilars market has experienced notable growth since 2017, with approval of several monoclonal antibody biosimilars in the US and Europe. This trend is expected to continue. Increased regulatory and legal activity related to the launch and approval of these therapeutics is anticipated. Regulatory authorities in other territories continue to implement or consider abbreviated approval processes for biosimilars, allowing quicker entry to market for such products and earlier than anticipated competition for patented biologics.

As well as facing generic competition upon expiry or loss of IP rights, we also face the risk that generic drug manufacturers seek to market generic versions of our products prior to expiries of our patents and/or the Regulatory Exclusivity periods. For example, we are currently facing challenges from numerous generic drug manufacturers regarding our patents relating to key products, including *Symbicort*, *Brilinta*, *Faslodex* and *Farxiga*.

IP rights protecting our products may be challenged by external parties. We expect our most valuable products to receive the greatest number of challenges. Despite our efforts to establish and defend robust patent protection for our products, we bear the risk that courts may decide that our IP rights are invalid and/or that third parties do not infringe our asserted IP rights.

Where we assert our IP rights but are ultimately unsuccessful, third parties may seek damages, alleging, for example, that they have been inappropriately restrained from entering the market. In such cases, we bear the risk that we incur liabilities to those third parties.

Details of material patent litigation matters can be found in Note 29 to the Financial Statements from page 194.

If we are not successful in obtaining, maintaining, defending or enforcing our exclusive rights to market our products, particularly in the US where we achieve our highest Product Sales, our revenue and margins could be materially adversely affected. In addition, unsuccessful assertion of our IP rights may lead to damages or other liabilities to third parties that could materially adversely affect our financial performance.

Approval of competitive products for the same or similar indication as one of our products may result in immediate and significant decreases in our revenues.

Unfavourable resolution of current and potential future patent litigation may require us to make significant provisions in our accounts relating to legal proceedings and/or could materially adversely affect our financial condition or results of operations.

Commercialisation risks	Impact

Price controls and reductions

Most of our key markets have experienced the implementation of various cost control or reimbursement mechanisms for pharmaceutical products.

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 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 payers to limit the use of branded products and put pressure on manufacturers to reduce net prices. In addition, patients are seeing changes in the design of their health plan benefits and may experience variation in how their plans cover their medications, including increases in the out-of-pocket payments for their branded medications. Patient out-of-pocket spending is generally in the form of a co-payment or co-insurance, but there is a growing trend towards high deductible health plans that require that patients pay the full list price of their drugs and services until they meet certain out-of-pocket thresholds. The US political landscape continues to consider a range of legislative and regulatory proposals to address the high costs of prescription drugs as well as reforms to the US healthcare system. We face uncertainties due to federal legislative and administrative efforts to repeal, substantially modify or invalidate some or all of the provisions of the ACA. Additionally, there may be modifications to Medicare and other government programmes, price transparency requirements, and policies aimed at reducing drug list prices. For more information, please see Pricing of medicines in the Marketplace section from page 11. It is difficult to predict what specific proposals could be enacted and to determine the implications for the healthcare system and pharmaceutical industry. However, lowering drug costs remains a key campaign promise of the current administration and proposals that would significantly modify existing laws and regulations, including coverage and reimbursement of drugs in government programmes and policies relating to drug pricing, could affect private health insurance, coverage and reimbursement in Medicare, Medicaid and the health insurance exchange marketplaces, and other facets of the US healthcare market, with potentially significant impacts on the pharmaceutical industry.

Ongoing scrutiny of the US pharmaceutical industry, focused largely on pricing, is placing increased emphasis on the value of medications. This scrutiny will likely continue across many stakeholders, including policymakers and legislators.

In the US, consolidation among distributors, retail pharmacy chains and other purchasing organisations, including integration across the supply chain, creates concentration of credit risk and increasing potential for large integrated entities to exert more power in negotiations with AstraZeneca, which could result in margin erosion.

In Europe, the industry continues to be exposed to various *ad hoc* cost-containment measures and reference pricing mechanisms, which impact prices. There is a trend towards increasing transparency and comparison of prices among EU Member States which may eventually lead to a change in the overall pricing and reimbursement landscape. There is also a continued push across the EU to harmonise the Health Technology Assessment (HTA) review process. This could lead to an environment in the EU where medicines undergo duplicate HTA evaluations, both at an EU level and a country level, as it is unlikely organisations such as GBA in Germany or HAS in France would make changes to their systems.

In Emerging Markets, governments are increasingly controlling pricing in the self-pay sector and favouring locally manufactured drugs. In addition, the emergence of price referencing has been seen in some markets combined with a call from authorities to provide greater global price transparency.

Concurrently, many markets are adopting the use of HTA to provide a rigorous evaluation of the clinical efficacy of a product at, or post, launch. HTA evaluations are also increasingly being used to assess the clinical effect, as well as cost-effectiveness, of products in a particular health system. This comes as payers and policymakers attempt to increase efficiencies in the use and choice of pharmaceutical products.

A summary of the principal aspects of price regulation and how pricing pressures are affecting our business in our most important markets is set out in Pricing of medicines in the Marketplace section from page 11 and on the next page in the following risk factor.

Due to these pricing pressures, there will continue to be downward pressure on prices globally that will challenge the profitability levels of products in particular markets.

Any future replacement, modification or repeal of the ACA, or any significant spending reductions or cost controls affecting Medicare, Medicaid or other publicly funded or subsidised health programmes in the US, could adversely affect our business and financial results. The significant uncertainty about the future of the ACA, entitlement reform and healthcare laws in general in the US could have a material adverse effect on our results of operations, financial condition or business.

We expect that consolidation and integration of drug distributors, retail pharmacy chains, private insurers, managed care organisations and other purchasing organisations may continue to have an effect on pharmaceutical manufacturers, including us.

The potential duplication of HTA evaluations could result in a delay to times of reimbursement and patient access.

The continued disparities in EU and US pricing systems could lead to marked price differentials between regions, which, by way of the implementation of existing or new reference pricing mechanisms, increases the pricing pressure affecting the industry. The importation of pharmaceutical products from countries where prices are low due to government price controls, or other market dynamics, to countries where prices for those products are higher, is already prevalent and may increase. Strengthened collaboration by governments may accelerate the development of further cost-containment policies (such as joint procurement). Increased and simplified access to national and regional prices in markets and the publication of these prices in centralised databases have facilitated the uptake and efficiency of price referencing across the world.

Commercialisation risks	Impact

Economic, regulatory and political pressures

Operating in over 100 countries, we are subject to political, socio-economic and financial factors (including foreign exchange movements) both globally and in individual countries.

A sustained global economic downturn may further exacerbate pressure from governments and other healthcare payers on medicine prices and volumes of sales in response to pressures on budgets, and may cause a slowdown or a decline in growth in some markets. Those most severely impacted by the economic downturn may seek alternative ways to settle their debts through, for example, the issuance of government bonds which might trade at a discount to the face value of the debt. Other customers may cease to trade, which may result in losses from writing off debts, or a reduction in demand for products.

We are highly dependent on being able to access a sustainable flow of liquid funds due to the high fixed costs of operating our business and the long and uncertain development cycles of our products. In a sustained economic downturn, financial institutions with whom we deal may cease to trade and there can be no guarantee that we will be able to access monies owed to us without a protracted, expensive and uncertain process, if at all.

The majority of our cash investments are managed centrally and are invested in collateralised bank deposits, fixed income securities in government, financial and non-financial securities, and AAA credit-rated institutional money market funds. Money market funds are backed by institutions in the US, EU or elsewhere, which, in turn, invest in other funds, including sovereign funds. This means our credit exposure is a mix of US, EU and rest of the world sovereign default risk, financial institution and non-financial institution default risk.

A number of our existing or future commercial or other agreements, such as borrowings, derivative financial instruments and commercial contracts, utilise or may utilise LIBOR or other similar rates as benchmark reference rates. LIBOR and other benchmark reference rates are the subject of ongoing national and international regulatory reform, the result of which could see them partially or fully replaced by alternative reference rates, with potential adjustments or renegotiations being necessary to our agreements in respect of the commercial terms or mechanisms to set the reference rate. Whilst different alternative reference rates could develop for different currencies and for different agreements, for example borrowings and derivative financial instruments, there is a risk that we fail to renegotiate our agreements. Any combination of these could have an adverse effect on the cost, cash flows, value, return on and trading market of (as appropriate) our borrowings, derivative financial instruments, commercial and other agreements, and could increase our administrative burden if the transition to alternative rates is required or necessary by regulation or market practice.

Deterioration of, or failure to improve, socio-economic conditions, and situations and/or resulting events, depending on their severity, could adversely affect our supply and/or distribution chain in the affected countries and the ability of customers or ultimate payers to purchase our medicines. This could adversely affect our business or results of operations.

While we have adopted cash management and treasury policies to manage the risk of not being able to access a sustainable flow of liquid funds (see the Financial risk management policies section of the Financial Review from page 86), we cannot be certain that these will be as effective as they are intended to be, in particular in the event of a global liquidity crisis. In addition, open positions where we are owed money and investments we have made in financial and non-financial institutions or money market funds cannot be guaranteed to be recoverable. Additionally, if we need access to external sources of financing to sustain and/or grow our business, such as the debt or equity capital financial markets, this may not be available on commercially acceptable terms, if at all, in the event of a severe and/or sustained economic downturn. This may, for instance, be the case in the event of any default by the Company on its debt obligations, which may materially adversely affect our ability to secure debt funding in the future or our financial condition in general. Further information on debt funding arrangements is contained in the Financial risk management policies section of the Financial Review from page 86.

In addition, as set out in the next section, the UK's exit from the EU due to take place on 29 March 2019 could adversely impact the operation of the financial system and the ability of financial institutions to perform certain activities and services upon which we rely.

Uncertainty and volatility in relation to the UK's planned exit from the EU

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). On 29 March 2017, the UK Government formally notified the EU under Article 50 of the UK's intention to leave the EU. This notification began the process of negotiation that will likely determine the future terms of the UK's relationship with the EU. Absent a negotiated agreement, the UK will leave the EU on 29 March 2019 and relevant EU law and agreements will cease to apply.

It is still too early to judge the full impact of Brexit. While a draft Withdrawal Agreement has been agreed between the UK government and the European Commission, it is 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 currently available including, for example, a no deal exit from the EU, extension or recission of the Article 50 notice and a second referendum. Brexit and implementation of the resulting changes could materially and adversely affect the tax, tax treaty, currency, operational, legal and regulatory regimes as well as the macro-economic environment in which the Group operates. Since the referendum, global markets and foreign exchange rates have experienced increased volatility, including a decline in the value of pound sterling as compared to the euro and US dollar. Upon leaving the EU, among other things, the UK could lose access to the single EU market, travel between the UK and EU countries could be restricted and border checks or other regulatory constraints may impede the free movement of goods. Our workforce, and in turn our ability to recruit and retain talent, could be impacted by any restrictions on the movement of persons as 3.9% of our employees in the UK are citizens of EU countries other than the UK. We could face new and greater costs and challenges if UK regulations and policies that govern our business diverge from those of the EU, or if there is any other new or increased friction in our trading environment.

Until the Brexit negotiation process is completed, it is difficult to anticipate the potential impact on our market share, sales, profitability and results of operations. For example, it is possible in the immediate aftermath of the UK leaving the EU that the capacity at major ports both in the UK and the EU is materially reduced for an indeterminate period of time. This could adversely affect our ability to transport medicines and raw materials/intermediates to the EU and *vice versa* with a consequential adverse impact.

The longer-term effects of Brexit are difficult to predict but could include further financial instability and slower economic growth or economic downturn in the UK in particular, but also in Europe and the global economy. Any restrictions on the movement of persons, deterioration in market access or trading terms, delay or restrictions to the movement of goods or increased cost and burdens in the form of new or diverging rules and regulations may have a significant adverse impact on our operations, profitability and business model. Further, uncertainty around the form and timing of any withdrawal agreement and the form and timing of any post-withdrawal trading arrangements (whether with the EU or third parties) could increase volatility and lead to adverse effects on the economy of the UK, other parts of Europe and the rest of the world, which in turn could have an adverse economic impact on our operations.

Commercialisation risks	Impact

Failures or delays in the quality and execution of our commercial strategies

Commercial success of our products and markets, including the development of growth markets, is a critical factor in sustaining or increasing global Product Sales and replacing lost Product Sales due to patent expiry. The successful launch of a new pharmaceutical product involves substantial investment in sales and marketing activities, launch stocks and other items. We may ultimately be unable to achieve commercial success for various reasons, including difficulties in manufacturing sufficient quantities of the product candidate for development or commercialisation in a timely manner, the impact of price control measures imposed by governments and healthcare authorities, the outcome of negotiations with third-party payers, erosion of IP rights, including infringement by third parties, failure to show a differentiated product profile and changes in prescribing habits.

The commercialisation of biologics is often more complex than for small molecule pharmaceutical products, primarily due to differences in the mode of administration, technical aspects of the product, and rapidly changing distribution and reimbursement environments.

We face particular challenges in Emerging Markets, including:

> More volatile economic conditions and/or political environments.
> Competition from multinational and local companies with existing market presence.
> Difficulties enforcing and protecting IP.
> Inadequate protection against crime (including counterfeiting, corruption and fraud).
> The need to impose developed market compliance standards.
> The need to meet a more diverse range of national regulatory, clinical, manufacturing and distribution requirements.
> Potential inadvertent breaches of local and international law and the need to manage sanctions and other restrictions that may be imposed in each jurisdiction.
> Recruitment of appropriately skilled and experienced personnel.
> Difficulty in identifying the most effective sales and marketing channels and routes to market.
> Intervention by local or national governments, or regulators, restricting market access and/or introducing adverse price controls.
> Difficulty in managing local partnerships such as co-promotion and co-marketing, in terms of performance, and adherence to AstraZeneca's compliance standards which are often higher than the market norm.
> Difficulties in cash repatriation due to strict foreign currency controls, risk of material currency devaluation and lack of hard currency reserves in some Emerging Markets.
> Complexity derived from direct exports to countries where we do not have a legal entity.

We may also seek to acquire complementary businesses or enter into other strategic transactions. The integration of an acquired business could involve incurring significant debt and unknown or contingent liabilities, as well as having a negative effect on our reported results of operations from acquisition-related charges, amortisation of expenses related to intangibles and charges for the implementation of long-term assets. The integration of new businesses with our own could result in operational complexities.

We may also experience difficulties in integrating geographically separated organisations, systems and facilities, and personnel with different organisational cultures. Disputes or difficulties in our relationship with our collaborators or partners may also arise, often due to conflicting priorities or conflicts of interest between parties.

Failure to execute our commercial strategies could materially adversely impact our business or results of operations.

If a new product does not succeed as anticipated or its rate of sales growth is slower than anticipated, there is a risk that we may be unable to fully recoup the costs incurred in launching it, which could materially adversely affect our business or results of operations.

Due to the complexity of the commercialisation process for biologics, the methods of distributing and marketing biologics could materially adversely impact our revenues from the sales of biologic medicines, such as *Synagis* and *FluMist/Fluenz*.

The failure to exploit potential opportunities appropriately in Emerging Markets or materialisation of the risks and challenges of doing business in such markets, including inadequate protection against crime (including counterfeiting, corruption and fraud) or inadvertent breaches of local and international law may materially adversely affect our reputation, business or results of operations.

Integration processes relating to strategic transactions may also result in business disruption, diversion of management resources, the loss of key employees and other issues, such as a failure to integrate IT and other systems.

Incurrence of significant debt or liabilities due to the integration of an acquired business could cause deterioration in our credit rating and result in increased borrowing costs and interest expense. We may issue additional shares to pay for acquired businesses, which would result in the dilution of the rights of our then existing shareholders.

Supply chain and business execution risks	Impact

Failure to maintain supply of compliant, quality products

We may experience difficulties, delays and interruptions in the manufacturing and supply of our products for various reasons, including:

- Demand significantly in excess of forecast demand, which may lead to supply shortages (this is particularly challenging before launch).
- Supply chain disruptions, including those due to natural or man-made disasters at one of our facilities, at a critical supplier or vendor, or during transit.
- Delays in construction of new facilities or the expansion of existing facilities, including those intended to support future demand for our products (particularly as the complexities associated with biologics facilities, especially for drug substances, increase the probability of delay).
- The inability to supply products due to a product quality failure or regulatory compliance action such as licence withdrawal, product recall or product seizure.
- Other manufacturing or distribution problems, including changes in manufacturing production sites, limits to manufacturing capacity due to regulatory requirements, changes in the types of products produced, or physical limitations or other business interruptions that could impact continuous and adequate supply.

As with the rest of the pharmaceutical industry, we work in a heavily regulated environment. It is necessary for us to meet all regulations, including compliance with Good Manufacturing Practices (GMP) and Good Distribution Practices (GDP) and comparable regulatory dossier conditions of approval in other countries in which our products are licensed, manufactured or sold. Regulatory agencies periodically inspect our manufacturing facilities to evaluate compliance with applicable requirements and may identify potential deficiencies.

We increasingly rely on third parties for the timely supply of goods, such as raw materials (for example, the API in some of our medicines and drug substances and/or finished drug products for some of our biologic medicines), equipment, formulated drugs and packaging, critical product components and services, all of which are key to our operations. Many of these goods are difficult to substitute in a timely manner or at all. We expect that external capacity for biologics drug substance production will remain constrained for the next few years and, accordingly, may not be readily available for supplementary production in the event that we experience an unforeseen need for such capacity.

Difficulties with manufacturing and supply, forecasting, distribution or third-party suppliers may result in product shortages, which may lead to lost Product Sales and materially adversely affect our reputation and revenues. Even slight variations in components or any part of the manufacturing process may lead to a product that is non-compliant and does not meet quality standards. This could lead to recalls, spoilage, product shortage, regulatory action and/or reputational harm.

Failure to comply with all manufacturing regulations can result in negative regulatory inspection findings leading to manufacturing cessation, product seizure, debarment or recalls which could have a material adverse effect on our business, financial condition and results of operations.

Illegal trade in our products

The illegal trade in pharmaceutical products is widely recognised by industry, non-governmental organisations and governmental authorities to be increasing. Illegal trade includes counterfeiting, theft and illegal diversion (that is, when our products are found in a market where we did not send them and where they are not approved or not permitted/allowed to be sold). There is a risk to public health when illegally traded products enter the supply chain, as well as associated financial risk. Authorities and the public expect us to help reduce opportunities for illegal trade in our products through securing our supply chains, surveillance, investigation and supporting legal action against those found to be engaged in illegal trade.

Public loss of confidence in the integrity of pharmaceutical products as a result of illegal trade could materially adversely affect our reputation and financial performance. In addition, undue or misplaced concern about this issue may cause some patients to stop taking their medicines, with consequential risks to their health. Authorities may take action, financial or otherwise, if they believe we are liable for breaches in our own supply chains.

There is also a direct financial loss when, for example, counterfeit and/or illegally diverted products replace sales of genuine products in a market or genuine products are recalled following discovery of counterfeit products.

Reliance on third-party goods and services

AstraZeneca spends approximately $10 billion each year with trade suppliers. The spend supports the length of our value chain from discovery to manufacture and commercialisation of our medicines.

Many of our business-critical operations, including certain R&D processes, IT systems, HR, finance, tax and accounting services have been outsourced to third-party providers. We are therefore heavily reliant on these third parties not just to deliver timely and high quality services, but also to comply with applicable laws and regulations and adhere to our ethical business expectations of third-party providers.

The failure of outsource providers to deliver timely services, and to the required level of quality, or the failure of outsource providers to co-operate with each other, could materially adversely affect our financial condition or results of operations. Moreover, the failure of these third parties to operate in an ethical manner could adversely impact our reputation, both internally and externally, or even result in non-compliance with applicable laws and regulations.

Our business and financial results could also be materially adversely affected by disruptions caused by our failure to successfully manage either the integration of outsourced services or the transition process of insourcing services from third parties.

Supply chain and business execution risks	Impact

Failure of information security, data protection and cybercrime

We are dependent on effective IT systems. These systems support key business functions such as our R&D, manufacturing, supply chain and sales capabilities. They provide an important means of safeguarding and communicating data, including critical or sensitive information, the confidentiality and integrity of which we rely on. We also rely on the effectiveness of our internal policies, controls and procedures to protect the confidentiality, integrity and availability of information held on our IT systems, as well as the effectiveness of our due diligence of, and ongoing oversight over, third-party vendors who hold or have access to our data. In addition, we must ensure that the personal data which we, or third-party vendors operating on our behalf, hold and process is protected in a manner that complies with the GDPR which entered into force in May 2018.

Examples of sensitive information that we protect include clinical trial records (patient names and treatments), personal information (employee bank details, home address), IP related to manufacturing process and compliance, key research science techniques, AstraZeneca property (ie, from theft) and privileged access (rights to perform IT tasks).

The size and complexity of our IT systems and cloud utilisation, and those of our third-party vendors (including outsource and Software as a Service (SaaS) providers) with whom we contract, have significantly increased over the past decade. Such systems are potentially vulnerable to service interruptions and security breaches from attacks by malicious third parties, or from intentional or inadvertent actions by our employees or vendors.

Significant changes in the business footprint and the implementation of the IT strategy, including the creation and use of captive offshore Global Technology Centres, could lead to temporary loss of capability.

We increasingly use the internet, digital content, social media, mobile applications, the internet of things (IoT), and other forms of new technology to communicate internally and externally. The accessibility and instantaneous nature of interactions with such media may facilitate or exacerbate the risk of unauthorised data loss from within AstraZeneca. It may also lead to false or misleading statements being made about AstraZeneca, which may damage our reputation, brand image or goodwill. As existing social media platforms expand and evolve, and new social media platforms emerge, it becomes increasingly challenging to identify new points of entry and to put structures in place to secure and protect sensitive information.

The GDPR and similar privacy legislation being passed in various jurisdictions globally introduce the obligation to report data protection breaches, whether intentional or inadvertent, to regulators and affected individuals within expedited timeframes. Such expedited reporting, often before the nature and impact of a data breach can be fully understood, could potentially cause reputational damage and a loss of public trust that ultimately may be disproportionate to the extent of the breach.

Any significant disruption to these IT systems (including breaches of data security or cybersecurity, failure to integrate new and existing IT systems) or failure to comply with additional requirements under the GDPR and other applicable laws, could harm our reputation and materially adversely affect our financial condition or results of operations.

While we invest heavily in the protection of our data and IT, we may be unable to prevent breakdowns or breaches in our systems or failures of our cybersecurity policies, controls or procedures. Any such breakdown, breach or failure could result in disclosure of confidential or other sensitive information, damage to our reputation, regulatory penalties, or sanctions, financial losses and/or other costs.

The inability to effectively back up and restore data could lead to permanent loss of data that could in turn result in non-compliance with applicable laws and regulations, and otherwise harm our business.

We and our vendors could be susceptible to third-party or internal attacks on our information security systems. Such attacks are of ever-increasing levels of sophistication and are made by groups and individuals with a wide range of motives and expertise, including organised criminal groups, 'hacktivists', nation states, employees and others. From time to time we experience intrusions, including as a result of computer-related malware. We may be unable to ward off such attacks which could have an adverse effect on our business.

Although we maintain cybersecurity insurance, there can be no assurance that our insurance coverage limits will protect against any future claim or that such insurance proceeds will be paid to us in a timely manner.

Inappropriate use of certain media vehicles could lead to the unauthorised or unintentional public disclosure of sensitive information (such as personally identifiable information on employees, healthcare professionals or patients, such as those enrolled in our clinical trials), which may damage our reputation, adversely affect our business or results of operations and expose us to legal risks and/or additional legal obligations. Similarly, the involuntary public disclosure of commercially sensitive information, or an information loss, could adversely affect our business or results of operations. In addition, negative posts or comments about us (or, for example, the safety of our products) on social media websites or other digital channels could harm our reputation, brand image or goodwill.

Failure of critical processes

Unexpected events and/or events beyond our control could result in the failure of critical processes within the Company or at third parties on whom we are reliant. The business faces threats to business continuity from many directions. Examples of material threats include:

> Disruption to our business or the global markets if there is instability in a particular geographic region, including as a result of war, terrorism, pandemics, armed conflicts, riots, unstable governments, civil insurrection or social unrest.
> Natural disasters in areas of the world prone to extreme weather events and earthquakes.
> Cyber threats similar to those detailed in the Failure of information security, data protection and cybercrime section above.

Failure of critical processes may result in an inability to research, manufacture or supply products to patients. AstraZeneca has developed a Business Resilience framework which is designed to mitigate such risks. However, there is no guarantee that these measures will be sufficient to prevent business interruption. This may expose the Company to litigation and/or regulatory action which may result in fines, loss of revenue and adversely affect the Company's financial results.

Any expected gains from productivity initiatives are uncertain

We continue to implement various productivity initiatives and restructuring programmes with the aim of enhancing the long-term efficiency of the business. However, anticipated cost savings and other benefits from these programmes are based on estimates and the actual savings may vary significantly or may not be achieved at all. In particular, these cost-reduction measures are often based on current conditions and cannot always take into account any future changes to the pharmaceutical industry or our operations, including new business developments or wage or price increases.

Our failure to successfully implement these planned cost-reduction measures, either through the successful implementation of employee relations processes (including consultation, engagement, talent management, recruitment and retention), or the possibility that these efforts do not generate the level of cost savings we anticipate, could materially adversely affect our business or results of operations.

Supply chain and business execution risks	Impact

Failure to attract and retain key personnel, and engage successfully with our employees

We rely heavily on recruiting and retaining talented employees with a diverse range of skills and capabilities to meet our strategic objectives.

We face intense competition for well-qualified individuals, as the supply of people with specific skills and significant leadership potential or in specific geographic regions may be limited, and in the UK the added uncertainty created by Brexit could impact the hiring and retention of staff in some business-critical areas.

The successful delivery of our business objectives is dependent on high levels of engagement, commitment and motivation of the workforce. 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. Such changes may increase levels of employee uncertainty leading to lower levels of engagement.

The inability to attract and retain highly-skilled personnel may weaken our succession plans for critical positions in the medium term, may materially adversely affect the implementation of our strategic objectives and could ultimately impact our business or results of operations.

Failure to engage effectively with our employees could lead to business disruption in our day-to-day operations, reduce levels of productivity and/or increase levels of voluntary turnover, all of which could ultimately materially adversely affect our business or results of operations.

Legal, regulatory and compliance risks	Impact

Failure to adhere to applicable laws, rules and regulations

Our many business operations are subject to a wide range of laws, rules and regulations from governmental and non-governmental bodies around the world.

Any failure to comply with these applicable laws, rules and regulations may result in us being investigated by relevant agencies and authorities and/or in legal proceedings being filed against us. Such investigations or proceedings could result in us becoming subject to civil or criminal sanctions and/or being forced to pay fines or damages. Relevant authorities have wide-ranging administrative powers to deal with any failure to comply with continuing regulatory oversight and this could affect us, whether such failure is our own or that of our contractors or external partners. Moreover, such laws, rules and regulations are subject to change.

Material examples of statutes, rules and regulations impacting business operations include:

- Compliance with Good Manufacturing Practice.
- Local, national and international environmental and occupational health and safety laws and regulations.
- Trade control laws governing our imports and exports including nationally and internationally recognised trade agreements, embargoes, trade and economic sanctions and anti-boycott requirements.
- Competition laws and regulations, including challenges from competition authorities and private damages actions.
- Rules and regulations established to promote ethical supply chain management.
- Financial regulations including, but not limited to, external financial reporting, taxation and money laundering.
- Employment practices.
- Disclosure of payments to healthcare professionals under the Sunshine Act and EFPIA legislation.
- Appropriate disclosure of community support, patient group support and product donations.
- Compliance with human rights and appropriate environmental practices of third-party contractors around the world including with, but not limited to, the conflict minerals rule in the US, and the UK Modern Slavery Act.

We have environmental and/or occupational health and safety-related liabilities at some current, formerly owned, leased and third-party sites. For more information on the most significant of these and for details on other significant litigation matters, please refer to Note 29 to the Financial Statements from page 194.

Failure to comply with applicable laws, rules and regulations; manage our liabilities; or to adequately anticipate or proactively manage emerging policy and legal developments could materially adversely affect our licence to operate or results of operations; adversely affect our reputation; cause harm to people or the environment; and/or lead to fines or other penalties.

For example, once a product has been approved for marketing by the regulatory authorities, it is subject to continuing control and regulation, such as the manner of its manufacture, distribution, marketing and safety surveillance. If regulatory issues concerning compliance with environmental, current Good Manufacturing Practice or safety monitoring regulations for pharmaceutical products (often referred to as pharmacovigilance) arise, this could lead to product recalls, loss of product approvals and seizures, and interruption of production, which could create product shortages and delays in new product approvals, and negatively impact patient access. As another example, violation of laws, rules, regulations or policies in countries subject to trade and economic sanctions could lead to loss of import or export privileges, civil or criminal penalties for us or our employees, or potential reputational harm, which could have a material adverse effect on our results of operations, financial condition or business.

Safety and efficacy of marketed products is questioned

Our ability to accurately assess, prior to launch, the eventual safety or efficacy of a new product once in broader clinical use can only be based on data available at that time, which is inherently limited due to relatively short periods of product testing and relatively small clinical study patient samples.

Any unforeseen safety concerns or adverse events relating to our products or failure to comply with laws, rules and regulations relating to provision of appropriate warnings concerning the dangers and risks of our products that result in injuries could expose us to large product liability damages claims, settlements and awards, particularly in the US. Adverse publicity relating to the safety of a product or of other competing products may increase the risk of product liability claims.

Details of material product liability litigation matters can be found in Note 29 to the Financial Statements from page 194.

Serious safety concerns or adverse events relating to our products could lead to product recalls, seizures, loss of product approvals, declining sales and interruption of supply and could materially adversely impact patient access, our reputation and financial revenues.

Significant product liability claims could also arise which could be costly, divert management attention, or damage our reputation and demand for our products.

Unfavourable resolution of such current and similar future product liability claims could subject us to enhanced damages, consumer fraud and/or other claims, including civil and criminal governmental actions, require us to make significant provisions in our accounts relating to legal proceedings, and could materially adversely affect our financial condition or results of operations, particularly where such circumstances are not covered by insurance. For more information, see the limited third party insurance coverage risk on page 230.

Legal, regulatory and compliance risks	Impact

Adverse outcome of litigation and/or governmental investigations

We may be subject to various product liability, consumer, commercial, anti-trust, environmental, employment or tax litigation or other legal proceedings and governmental investigations. Litigation, particularly in the US, is inherently unpredictable and unexpectedly high awards for damages can result from an adverse verdict. In many cases, plaintiffs may claim enhanced damages in extremely high amounts. In particular, the marketing, promotional, clinical and pricing practices of pharmaceutical manufacturers, as well as the manner in which manufacturers interact with purchasers, prescribers and patients, are subject to extensive regulation, litigation and governmental investigation. Many companies, including AstraZeneca, have been subject to claims related to these practices asserted by federal and state governmental authorities and private payers and consumers, which have resulted in substantial expense and other significant consequences. Note 29 to the Financial Statements from page 194 describes the material legal proceedings in which we are currently involved.

Governmental investigations, for example under the US Foreign Corrupt Practices Act or federal or state False Claims Acts or other types of legal proceedings, regardless of their outcome, could be costly, divert management attention, or damage our reputation and demand for our products. Unfavourable resolution of current and similar future proceedings against us could subject us to criminal liability, fines, penalties or other monetary or non-monetary remedies, including enhanced damages, require us to make significant provisions in our accounts relating to legal proceedings and could materially adversely affect our business or results of operations.

Failure to adhere to increasingly stringent anti-bribery and anti-corruption legislation

There remains an increased global focus on the implementation and enforcement of anti-bribery and anti-corruption legislation.

Two relevant pieces of legislation include the UK Bribery Act and the US Foreign Corrupt Practices Act, and many other countries where we operate are also enforcing their own laws more aggressively and/or adopting tougher new measures. There has also been an increase in co-operation and co-ordination between regulators across countries with respect to investigation and enforcement.

We have been the subject of anti-corruption investigations and there can be no assurance that we will not, from time to time, be subject to informal enquiries and formal investigations from governmental agencies. In the context of our business, governmental officials interact with us in various roles that are important to our operations, such as in the capacity of a regulator, partner or healthcare payer, reimburser or prescriber, amongst others. To the extent we are the subject of any such pending and material matters, details are included in Note 29 to the Financial Statements from page 194.

Despite taking measures to prevent breaches of applicable anti-bribery and anti-corruption laws by our personnel and associated third parties, breaches may still occur, potentially resulting in the imposition of significant penalties, such as fines, the requirement to comply with monitoring or self-reporting obligations, or debarment or exclusion from government sales or reimbursement programmes, any of which could materially adversely affect our reputation, business or results of operations.

Economic and financial risks	Impact

Failure to achieve strategic plans or meet targets and expectations

From time to time, we communicate our business strategy or our targets or expectations regarding our future financial or other performance (for example, the expectations described in Future prospects in the Financial Review on page 86). All such statements are of a forward-looking nature and are based on assumptions and judgements we make, all of which are subject to significant inherent risks and uncertainties, including those that we are unaware of and/or that are beyond our control.

There can be no guarantee that our financial targets or expectations will materialise on the expected timeline or at all. Actual results may deviate materially and adversely from any such target or expectation, including if one or more of the assumptions or judgements underlying any such target or expectation proves to be incorrect in whole or in part.

Any failure to successfully implement our business strategy, whether determined by internal or external risk factors, may frustrate the achievement of our financial or other targets or expectations and, in turn, materially damage our brand and materially adversely affect our business, financial position or results of operations.

Failure in financial control or the occurrence of fraud

Effective internal controls are necessary for us to provide reliable financial reports and are designed to prevent and detect fraud. Lapses in controls and procedures could undermine the ability to prevent fraud or provide accurate disclosure of financial information on a timely basis. Testing of our internal controls can provide only reasonable assurance with respect to the preparation and fair presentation of financial statements and may not prevent or detect misstatements or fraud.

Significant resources may be required to remediate any lapse or deficiency in internal controls.

Any such deficiency may also trigger investigations by a number of organisations, for example, the SEC, the DOJ or the UK Serious Fraud Office and may result in fines being levied against Group individual directors or officers.

Serious fraud may lead to potential prosecution or even imprisonment of senior management.

Economic and financial risks	Impact

Unexpected deterioration in the Group's financial position

A wide range of financial risks could result in a material deterioration in the Group's financial position.

As a global business, currency fluctuations can significantly affect our results of operations, which are reported in US dollars. Approximately 33% of our global 2018 Product Sales were in the US, which is expected to remain our largest single market for the foreseeable future. Product Sales in other countries are predominantly in currencies other than the US dollar, including Chinese renminbi, the euro, Japanese yen and pound sterling.

Our consolidated balance sheet contains significant investments in intangible assets, including goodwill. The nature of the pharmaceutical business is high risk and requires that we invest in a large number of projects in an effort to develop a successful portfolio of approved products. Our ability to realise value on these significant investments is often contingent upon, among other things, regulatory approvals, market acceptance, competition and legal developments. As such, in the course of our many acquisitions and R&D activities, we expect that some of our intangible assets will become impaired and be written off at some time in the future.

Inherent variability of biologics manufacturing increases the risk of write-offs of these product batches. Due to the value of the materials used, the carrying amount of biologic products is much higher than that of small molecule products. As we continue to grow our biologics business, we also increase the risk of potential impairment charges.

The costs associated with product liability litigation have increased the cost of, and narrowed the coverage afforded by, pharmaceutical companies' product liability insurance. To contain insurance costs, as of February 2006, we adjusted our product liability coverage profile, accepting uninsured exposure above $100 million. In addition, where claims are made under insurance policies, insurers may reserve the right to deny coverage on various grounds. For example, product liability litigation cases relating to *Farxiga* and *Nexium* in the US are not covered by third-party product liability insurance. See Note 29 to the Financial Statements from page 194 for details.

The integrated nature of our worldwide operations can produce conflicting claims from revenue authorities as to the profits to be taxed in individual countries. The majority of the jurisdictions in which we operate have double tax treaties with other foreign jurisdictions, which provide a framework for mitigating the incidence of double taxation on our revenues and capital gains.

The Group's worldwide operations are taxed under laws in the jurisdictions in which they operate. International standards governing the global tax environment regularly change. The Organisation for Economic Co-operation and Development (OECD) has proposed a number of changes under the Base Erosion and Profit Shifting (BEPS) Action Plans which are now being progressively implemented by tax authorities around the world.

Our defined benefit pension obligations are largely backed by assets invested across the broad investment market. Our most significant obligations relate to defined benefit pension funds in the UK, Sweden and the US. The largest obligation is in the UK.

Movements in the exchange rates used to translate foreign currencies into US dollars may materially adversely affect our financial condition or results of operations. Some of our subsidiaries import and export goods and services in currencies other than their own functional currency, and so the financial results of such subsidiaries could be affected by currency fluctuations arising between the transaction and settlement dates. In addition, there are foreign exchange differences arising on the translation of investments in subsidiaries.

We have significant investments in goodwill and intangible assets as a result of our acquisitions of various businesses and our purchases of certain assets, such as product development and marketing rights. Impairment losses may materially adversely affect our financial condition or results of operations. Details of the carrying values of goodwill and intangible assets, and the estimates and assumptions we make in our impairment testing, are included in Notes 8 and 9 to the Financial Statements from page 168.

Financial liabilities arising due to product liability or other litigation, in respect of which we do not have insurance coverage, or if an insurer's denial of coverage is ultimately upheld, could require us to make significant provisions relating to legal proceedings and could materially adversely affect our financial condition or results of operations.

For more information, please see the Adverse outcome of litigation and/or governmental investigations risk on page 229.

The resolution of tax disputes regarding the profits to be taxed in individual territories can result in a reallocation of profits between jurisdictions and an increase or decrease in related tax costs, and has the potential to affect our cash flows, EPS and post-tax earnings. Claims, regardless of their merits or their outcome, are costly, divert management attention and may adversely affect our reputation.

If any double tax treaties are withdrawn or amended, especially in a territory where a member of the AstraZeneca Group is involved in a taxation dispute with a tax authority in relation to cross-border transactions, such withdrawal or amendment could materially adversely affect our financial condition or results of operations, as could a negative outcome of a tax dispute or a failure by tax authorities to agree through competent authority proceedings. Changes to the application of double tax treaties, as a result of the parent company of the Group no longer being an EU entity following Brexit, could also result in adverse consequences such as those described above. See the Financial risk management policies section of the Financial Review on page 86 for tax risk management policies and Note 29 to the Financial Statements from page 194 for details of current tax disputes.

Changes in tax regimes, such as those relating to the US federal tax regime which were effective from 1 January 2018, could result in a material impact on the Group's cash tax liabilities and tax charge, resulting in either an increase or a reduction in financial results depending upon the nature of the change. We represent views to the OECD, governments and tax authorities through public consultations to ensure international institutions and governments understand the business implications of proposed law changes. Specific OECD BEPS recommendations that we expect to impact the Group include changes to patent box regimes, restrictions of interest deductibility and revised transfer pricing guidelines.

Sustained falls in asset values could reduce pension fund solvency levels, which may result in requirements for additional cash, restricting the cash available for our business. Changes to funding regulations for defined benefit pensions may also result in a requirement for additional cash contributions by the Group. If the present value of the liabilities increases due to a sustained low interest rate environment, an increase in expectations of future inflation, or an improvement in member longevity (above that already assumed), this could also reduce pension fund solvency ratios. The likely increase in the IAS 19 accounting deficit generated by any of these factors may cause the credit rating agencies to review our credit rating, with the potential to negatively affect our ability to raise debt and the price of new debt issuances. See Note 21 to the Financial Statements from page 178 for further details of the Group's pension obligations.

Sustainability: supplementary information

External assurance

Bureau Veritas has provided independent external assurance to a limited level on the following sustainability information contained within this Annual Report:

> Key Performance Indicators – Be a Great Place to Work, page 22
> Key Performance Indicators – Do business sustainably, page 22
> Emerging market healthcare, page 32
> Develop a strong and diverse pipeline of leaders, page 40
> Human rights, page 41
> Managing change, page 41
> Employee relations, page 41
> Safety, health and wellbeing, page 41
> Sustainability, page 42
> Sustainability strategy, page 42
> Sustainability governance, page 43
> Broadening access to healthcare, page 43
> Ethics and transparency, page 43
> Protecting the environment, page 46
> Community investment, page 48
> Young Health Programme, page 48
> Donation programmes, page 48
> Greenhouse gas (GHG) reporting, page 231

Based on the evidence provided and subject to the scope, objectives and limitations defined in the full assurance statement, nothing has come to the attention of Bureau Veritas causing them to believe that the sustainability information contained within this Annual Report is materially misstated. Bureau Veritas is a professional services company that has a long history of providing independent assurance services in environmental, health, safety, social and ethical management and disclosure.

The full assurance statement, which includes Bureau Veritas's scope of work, methodology, overall opinion, and limitations and exclusions, is available on our website, www.astrazeneca.com.

Greenhouse gas (GHG) reporting

We have reported on all of the emission sources required under the Quoted Companies Greenhouse Gas Emissions (Directors' Reports) Regulations 2013. These sources fall within our consolidated Financial Statements. We do not have responsibility for any emission sources that are not included in our consolidated Financial Statements.

We have used the GHG Protocol Corporate Accounting and Reporting Standard (revised edition). Emission factors for electricity have been derived from the International Energy Agency (IEA), USEPA eGRID, US Green-e and the Association of Issuing Bodies (AIB) databases and for all other fuels and emission sources from the 2006 IPCC Guidelines for National Greenhouse Gas Inventories.

Bureau Veritas has undertaken a limited assurance on the 2018 GHG emissions data. The assurance statement, including scope, methodology, overall opinion, and limitations and exclusions, is available on our website, www.astrazeneca.com.

Global greenhouse gas emissions data for the period 1 January 2018 to 31 December 2018[1]

	Tonnes CO_2e		
	2018	2017	2016
Emissions from: Scope 1: Combustion of fuel and operation of facilities[2]	**301,055**	291,694	309,685
Scope 2 (Market-based): Electricity (net of market instruments), heat, steam and cooling purchased for own use[3]	**158,987**	178,614	218,770
Scope 2 (Location-based): Electricity, heat, steam and cooling purchased for own use[3]	**294,906**	273,681	288,210
Company's chosen intensity measurement: Scope 1 + Scope 2 (Market-based) emissions reported above normalised to million US dollar revenue	**20.8**	20.9	23.0
Scope 3 in our Operational Footprint: Supply chain emissions: Upstream emissions from personal air travel, goods transport, waste incineration, and first tier active pharmaceutical ingredients and formulation & packaging suppliers (>90% of category spend, energy only, one year in arrears); Downstream emissions from HFA propellants released during patient use of our inhaled medicines	**1,309,069**	1,234,739	1,155,504
2016-2025 Strategy 'Operational Footprint' KPI: Scope 1 + Scope 2 (Market-based) + our Operational Footprint Scope 3 sources. Baseline year is 2015	**1,769,110**	1,705,047	1,683,959
Scope 3 Total: Emissions from all 15 Greenhouse Gas Protocol Scope 3 Categories[4]	**5,819,517**	5,830,380	5,813,138
2016-2025 Strategy Scope 3 intensity measurement KPI: Scope 3 emissions from all 15 Greenhouse Gas Protocol Scope 3 Categories normalised to million US dollar revenue. Baseline year is 2015 (one year in arrears)	**263**	260	253

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.

2 Included in this section are GHGs from direct fuel combustion, process and engineering emissions at our sites and from fuel use in our vehicle fleet.

3 GHGs from imported electricity are calculated using the GHG Protocol Scope 2 Guidance (January 2015) requiring the dual reporting using two emissions factors for each site – Market-based and Location-based. Our corporate emissions reporting and targets follow the Market-based approach.

4 In previous years, this data has been reported one year in arrears. GHG accounting has been updated to align the 2016 and 2017 reporting with the actual year's emissions data. For 2018 reporting, a significant proportion has been estimated and will be refined in future external reports.

Shareholder Information

The principal markets for trading in AstraZeneca shares are the London Stock Exchange, Nasdaq Stockholm and the New York Stock Exchange. Ordinary Shares of $0.25 each in AstraZeneca PLC are listed on the London Stock Exchange and the shareholder register is maintained by Equiniti Limited, the Ordinary Share registrar. Shares listed on Nasdaq Stockholm are issued under the Euroclear Services Agreement by Euroclear Sweden AB, the Swedish Central Securities Depositary. Shares listed on the New York Stock Exchange are in the form of American Depositary Shares (ADSs), evidenced by American Depositary Receipts (ADRs) issued by the Company's ADR depositary, Citibank, N.A. Two ADSs are equivalent to one Ordinary Share. Before 27 July 2015 the ratio was one ADS per one Ordinary Share.

Ordinary Share registrar

Equiniti Limited
Aspect House
Spencer Road
Lancing
West Sussex
BN99 6DA
UK
Tel (Freephone in UK): +44 (0)800 389 1580
Tel (outside UK): +44 (0)121 415 7033

Swedish Central Securities Depositary

Euroclear Sweden AB
PO Box 191
SE-101 23 Stockholm
Sweden
Tel: +46 (0)8 402 9000

ADR depositary

Citibank Shareholder Services
PO Box 43077
Providence
RI 02940-3077
USA
Tel (toll free in the US): +1 (888) 697 8018
Tel (outside the US): +1 (781) 575 4555
citibank@shareholders-online.com

Annual general meeting (AGM)

The 2019 AGM will be held on 26 April 2019. The meeting place will be in London, UK. Shareholders holding Ordinary Shares directly are entitled to attend and vote at the meeting or may submit a proxy voting instruction in advance, by following the instructions in the notice of AGM.

If you hold shares listed in Stockholm or hold ADRs, information relating to voting and attendance will be included in the relevant notice of AGM.

If you hold your shares through a nominee, your nominee provider will be able to advise you of their arrangements in relation to voting and attendance.

Dividends

Dividend dates for 2019 are shown in the financial calendar on page 233. A first interim dividend is normally announced in July/August and paid in September and a second interim dividend is normally announced in January/February and paid in March. Dividends are paid in GBP, SEK and USD, depending on where the eligible shares are listed. Further information on dividends declared can be found in the Shareholder Information section of AstraZeneca's website at www.astrazeneca.com.

Shareholders holding Ordinary Shares directly may opt for dividends to be paid straight to their bank or building society account, rather than being paid by cheque. To elect for this swift and secure method of payment, contact the Ordinary Share registrar, visit www.shareview.co.uk or fill in the mandate form that will be sent to you with your next dividend cheque. If you hold shares listed in Stockholm, you should contact your personal broker or, if you hold a VP account, contact the bank that services your VP account. If you hold ADRs directly you should contact Shareholder Services on the number provided. If you hold your shares through a nominee, you should direct any queries relating to your shareholding and dividend payments to the nominee provider.

Shareholder communications

Copies of shareholder communications and annual reports are available on AstraZeneca's website at www.astrazeneca.com. If you hold Ordinary Shares directly, currently receive hard copies of shareholder communications and/or the annual report and would rather receive these documents electronically, you can manage your communication preferences at www.shareview.co.uk or by contacting the Ordinary Share registrar. If your record on the Ordinary Share register has been duplicated you may receive multiple copies of shareholder communications; if this is the case please contact the Ordinary Share registrar so that this can be rectified.

Holders of shares listed in Stockholm should contact Computershare AB, PO Box 610, SE-182 16 Danderyd, Sweden (Tel: +46 (0)8 588 04 200) and holders of ADRs should contact the ADR depositary or their personal broker with queries relating to shareholder communications.

Shareview

Holders of Ordinary Shares may create a portfolio at www.shareview.co.uk to view and manage their AstraZeneca shareholding. Shareview is a free and secure online service provided by the Ordinary Share registrar that allows users to, among other things, update personal details, manage communication preferences, view dividend information and manage direct dividend payments.

ShareGift

Shareholders that hold only a small number of shares, the value of which makes it uneconomical to sell them, may wish to consider donating them to charity through ShareGift, an independent charity share donation scheme (registered charity number 1052686). Further information about ShareGift can be found on its website at www.sharegift.org or by calling +44 (0)20 7930 3737.

The Unclaimed Assets Register

AstraZeneca provides information to the Unclaimed Assets Register (UAR) relating to unclaimed dividends paid on Ordinary Shares. The UAR database provides a facility to search for financial assets that may have been forgotten and can be contacted on +44 (0)333 000 0182 or uarenquiries@uk.experian.com.

Shareholder fraud warning

Shareholders of AstraZeneca and many other companies have reported receiving unsolicited calls and correspondence relating to their shareholdings and investment matters. Shareholders are advised to be very cautious of any unsolicited approaches and to note that reputable firms authorised by the Financial Conduct Authority (FCA) are very unlikely to make such approaches. Such approaches are likely to be part of a 'boiler room scam' attempting to defraud shareholders.

Shareholders are advised to familiarise themselves with the information on scams available on the FCA website, www.fca.org.uk/consumers and within the FAQs in the Investors section of AstraZeneca's website, www.astrazeneca.com.

Any suspected scams or fraudulent approaches should be reported to the FCA via its website and to AstraZeneca's Ordinary Share registrar, using the contact details on this page.

Investor Relations

www.astrazeneca.com/investors
irteam@astrazeneca.com
Tel (UK): +44 (0)20 3749 5824
Tel (toll free in the US): +1 866 381 7277

Financial calendar

Event	Provisional date
Second interim dividend for 2018	
Ex-dividend date	28 February 2019
Record date	1 March 2019
Payment date	27 March 2019
Announcement of first quarter results for 2019	26 April 2019
Annual general meeting (AGM)	26 April 2019
Announcement of second quarter and half-year results for 2019	25 July 2019
First interim dividend for 2019	
Ex-dividend date	8 August 2019
Record date	9 August 2019
Payment date	9 September 2019
Announcement of third quarter results for 2019	24 October 2019
Financial year end	31 December 2019

History and development of the Company

AstraZeneca PLC was incorporated in England and Wales on 17 June 1992 under the Companies Act 1985. It is a public limited company domiciled in the UK. The Company's registered number is 2723534 and its registered office is at 1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge CB2 0AA, UK (Tel: +44 (0)20 3749 5000). From February 1993 until April 1999, the Company was called Zeneca Group PLC. On 6 April 1999, the Company changed its name to AstraZeneca PLC.

The Company was formed when the pharmaceutical, agrochemical and specialty chemical businesses of Imperial Chemical Industries PLC were demerged in 1993. In 1999, the Company sold the specialty chemical business. Also in 1999, the Company merged with Astra of Sweden. In 2000, it demerged the agrochemical business and merged it with the similar business of Novartis to form a new company called Syngenta AG. In 2007, the Group acquired MedImmune, a biologics and vaccines business based in the US.

In 1999, in connection with the merger between Astra and Zeneca, the Company's share capital was redenominated in US dollars. On 6 April 1999, Zeneca shares were cancelled and US dollar shares issued, credited as fully paid on the basis of one dollar share for each Zeneca share then held. This was achieved by a reduction of capital under section 135 of the Companies Act 1985. Upon the reduction of capital becoming effective, all issued and unissued Zeneca shares were cancelled and the sum arising as a result of the share cancellation credited to a special reserve, which was converted into US dollars at the rate of exchange prevailing on the record date. This US dollar reserve was then applied in paying up, at par, newly created US dollar shares.

At the same time as the US dollar shares were issued, the Company issued 50,000 Redeemable Preference Shares for cash, at par. The Redeemable Preference Shares carry limited class voting rights, no dividend rights and are capable of redemption, at par, at the option of the Company on the giving of seven days' written notice to the registered holder of the Redeemable Preference Shares.

A total of 826 million Ordinary Shares were issued to Astra shareholders who accepted the merger offer before the final closing date, 21 May 1999. The Company received acceptances from Astra shareholders representing 99.6% of Astra's shares and the remaining 0.4% was acquired in 2000, for cash.

Issued share capital, shareholdings and share prices

At 31 December 2018, the Company had 83,588 registered holders of 1,267,039,436 Ordinary Shares. There were 105,266 holders of Ordinary Shares held under the Euroclear Services Agreement, representing 10.1% of the issued share capital of the Company and 1,818 registered holders of ADSs, representing 20.1% of the issued share capital of the Company.

Ordinary Shares in issue

	2018	2017	2016	2015	2014
Ordinary Shares in issue – millions					
At year end	**1,267**	1,266	1,265	1,264	1,263
Weighted average for year	**1,267**	1,266	1,265	1,264	1,262
Stock market price per Ordinary Share (London Stock Exchange)					
Highest (pence)	**6317.0**	5508.0	5220.0	4863.0	4823.5
Lowest (pence)	**4712.5**	4194.0	3774.0	3903.5	3549.5
At year end (pence)	**5873.0**	5121.0	4437.5	4616.5	4555.5

Analysis of shareholdings as a percentage of issued share capital at 31 December

Number of Ordinary Shares[1]	**2018 %**	2017 %	2016 %	2015 %	2014 %
1 – 250	**0.4**	0.5	0.5	0.5	0.5
251 – 500	**0.5**	0.5	0.5	0.6	0.6
501 – 1,000	**0.5**	0.6	0.6	0.7	0.7
1,001 – 5,000	**0.8**	0.8	0.8	0.9	1.0
5,001 – 10,000	**0.2**	0.2	0.2	0.2	0.2
10,001 – 50,000	**1.0**	1.0	0.9	0.9	1.0
50,001 – 1,000,000	**12.1**	11.9	12.3	13.0	13.3
Over 1,000,000	**84.5**	84.5	84.2	83.2	82.7

[1] Includes Euroclear and ADR holdings.

Shareholder Information
continued

Reported high and low share prices during the year

		Ordinary Shares London Stock Exchange[1]		Ordinary Shares Nasdaq Stockholm[2]		ADRs New York Stock Exchange[3]	
		High (pence)	Low (pence)	High (SEK)	Low (SEK)	High (USD)	Low (USD)
2018	– December	6211.0	5720.0	722.0	661.8	39.87	36.86
	– November	6317.0	5732.0	754.8	692.4	41.49	37.85
	– October	6078.0	5546.0	725.0	665.5	40.08	37.15
	– September	5963.0	5572.0	702.1	659.6	39.72	37.07
	– August	6107.0	5795.0	721.8	680.7	39.61	37.96
	– July	5865.0	5182.0	685.3	608.2	39.13	34.76
	– Quarter 4	6317.0	5546.0	754.8	661.8	41.49	36.86
	– Quarter 3	6107.0	5182.0	721.8	608.2	39.72	34.76
	– Quarter 2	5478.0	4867.0	648.4	584.3	37.05	34.55
	– Quarter 1	5204.0	4712.5	587.3	531.7	36.63	32.97
2017	– Quarter 4	5180.0	4705.0	581.0	541.0	34.78	32.09
	– Quarter 3	5192.0	4325.0	578.0	466.2	34.16	28.88
	– Quarter 2	5508.0	4566.0	619.0	534.0	35.36	29.76
	– Quarter 1	4974.5	4194.0	558.0	470.6	31.80	26.72

[1] For shares listed on the London Stock Exchange, the reported high and low middle market closing quotations are derived from the Daily Official List.
[2] For shares listed on Nasdaq Stockholm, the high and low closing sales prices are as stated in the Official List.
[3] For ADRs listed on the New York Stock Exchange, the reported high and low sales prices are as reported by Dow Jones (ADR quotations).

US holdings

At 31 January 2019, the proportion of Ordinary Shares represented by ADSs was 20.0% of the issued share capital of the Company. At 31 January 2019, there were 83,479 registered holders of Ordinary Shares, of which 688 were based in the US and there were 1,813 record holders of ADRs, of which 1,785 were based in the US.

Major shareholdings

At 31 December 2018, the following persons had disclosed an interest in the issued Ordinary Share capital of the Company in accordance with the requirements of rules 5.1.2 or 5.1.5 of the UK Listing Authority's Disclosure Guidance and Transparency Rules:

Shareholder	Number of Ordinary Shares	Date of disclosure to Company[1]	**Number of Ordinary Shares disclosed as a percentage of issued share capital at 31 December 2018**
BlackRock, Inc.	100,885,181	4 December 2009	**7.96**
Investor AB	51,587,810	2 February 2012	**4.07**
The Capital Group Companies, Inc.	63,802,495	17 July 2018	**5.04**

[1] Since the date of disclosure to the Company, the interest of any person listed above in Ordinary Shares may have increased or decreased. No requirement to notify the Company of any increase or decrease arises unless the holding passes a notifiable threshold in accordance with rules 5.1.2 or 5.1.5 of the UK Listing Authority's Disclosure Guidance and Transparency Rules.

So far as the Company is aware, no other person held a notifiable interest in the issued Ordinary Share capital of the Company. No changes to major shareholdings were disclosed to the Company between 31 December 2018 and 31 January 2019.

Changes in the percentage ownerships disclosed by major shareholders during the past three years are set out below. Major shareholders do not have different voting rights.

Shareholder	**31 January 2019**	31 January 2018	31 January 2017	31 January 2016
BlackRock, Inc.	**7.96**	7.97	7.97	7.98
Investor AB	**4.07**	4.07	4.08	4.08
The Capital Group Companies, Inc.	**5.04**	4.98	3.00	3.00

So far as the Company is aware, it is neither directly nor indirectly owned or controlled by one or more corporations or by any government.

The Company does not know of any arrangements, the operation of which might result in a change in the control of the Company.

Directors' and officers' shareholdings

At 31 January 2019, the total amount of the Company's voting securities owned by Directors and officers of the Company was:

Title of class	Amount owned	Percentage of class
Ordinary Shares	**564,514**	**0.04**

Options to purchase securities from registrant or subsidiaries

(a) At 31 January 2019, options outstanding to subscribe for Ordinary Shares were:

Number of shares	Subscription price (pence)	Normal expiry date
1,689,933	**2280-4724**	**2019-2024**

The weighted average subscription price of options outstanding at 31 January 2019 was 3610 pence. All options were granted under Company employee share schemes.

(b) Included in paragraph (a) are options granted to officers of the Company as follows:

Number of shares	Subscription price (pence)	Normal expiry date
1,407	**3307-3597**	**2021**

(c) Details of Directors' option holdings are shown in the Remuneration Report on page 138. No options were held by Directors at 31 December 2018.

During the period 1 January 2019 to 31 January 2019, no Director was granted or exercised any options.

Related party transactions

During the period 1 January 2019 to 31 January 2019, there were no transactions, loans, or proposed transactions between the Company and any related parties which were material to either the Company or the related party, or which were unusual in their nature or conditions (see also Note 31 to the Financial Statements on page 200).

Articles of Association

AstraZeneca PLC's current Articles were adopted by shareholders at the Company's AGM held on 18 May 2018. Any amendment to the Articles requires the approval of shareholders by a special resolution at a general meeting of the Company.

Objects

The Company's objects are unrestricted.

Directors

The Board has the authority to manage the business of the Company, for example, through powers to allot and repurchase its shares, subject where required to shareholder resolutions. Subject to certain exceptions, Directors do not have power to vote at Board meetings on matters in which they have a material interest.

The quorum for meetings of the Board is a majority of the full Board, of whom at least four must be Non-Executive Directors. In the absence of a quorum, the Directors do not have power to determine compensation arrangements for themselves or any member of the Board.

The Board may exercise all the powers of the Company to borrow money. Variation of these borrowing powers would require the passing of a special resolution of the Company's shareholders.

All Directors must retire from office at the Company's AGM each year and may present themselves for election or re-election. Directors are not prohibited, upon reaching a particular age, from submitting themselves for election or re-election.

Rights, preferences and restrictions attaching to shares

As at 31 December 2018, the Company had 1,267,039,436 Ordinary Shares and 50,000 Redeemable Preference Shares in issue. The Ordinary Shares represent 99.98% and the Redeemable Preference Shares represent 0.02% of the Company's total share capital (these percentages have been calculated by reference to the closing mid-point USD/GBP exchange rate on 31 December 2018 as published in the London edition of the Financial Times newspaper).

As agreed by the shareholders at the Company's AGM held on 29 April 2010, the Articles were amended with immediate effect to remove the requirement for the Company to have an authorised share capital, the concept of which was abolished under the Companies Act 2006. Each Ordinary Share carries the right to vote at general meetings of the Company. The rights and restrictions attaching to the Redeemable Preference Shares differ from those attaching to Ordinary Shares as follows:

- The Redeemable Preference Shares carry no rights to receive dividends.
- The holders of Redeemable Preference Shares have no rights to receive notices of, attend or vote at general meetings except in certain limited circumstances. They have one vote for every 50,000 Redeemable Preference Shares held.
- On a distribution of assets of the Company, on a winding-up or other return of capital (subject to certain exceptions), the holders of Redeemable Preference Shares have priority over the holders of Ordinary Shares to receive the capital paid up on those shares.
- Subject to the provisions of the Companies Act 2006, the Company has the right to redeem the Redeemable Preference Shares at any time on giving not less than seven days' written notice.

There are no specific restrictions on the transfer of shares in the Company, which is governed by the Articles and prevailing legislation.

The Company is not aware of any agreements between holders of shares that may result in restrictions on the transfer of shares or that may result in restrictions on voting rights. The Company is also not aware of any arrangements under which financial rights are held by a person other than the holder of the shares.

Action necessary to change the rights of shareholders

In order to vary the rights attached to any class of shares, the consent in writing of the holders of three quarters in nominal value of the issued shares of that class or the sanction of a special resolution passed at a general meeting of such holders is required.

General meetings

AGMs require 21 clear days' notice to shareholders. Subject to the Companies Act 2006, other general meetings require 14 clear days' notice.

For all general meetings, a quorum of two shareholders present in person or by proxy, and entitled to vote on the business transacted, is required unless each of the two persons present is a corporate representative of the same corporation; or each of the two persons present is a proxy of the same shareholder.

Shareholders and their duly appointed proxies and corporate representatives are entitled to be admitted to general meetings.

Limitations on the rights to own shares

There are no limitations on the rights to own shares.

Shareholder Information
continued

Documents on display
The Articles and other documents concerning the Company which are referred to in this Annual Report may be inspected at the Company's registered office at 1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge CB2 0AA, UK.

Compliance requirements under Listing Rule 9.8.4
Other than as set out below, the Company has nothing to report under Listing Rule 9.8.4.

Item	Location of details in Annual Report
Details of any long-term incentive schemes	Note 28 of the Financial Statements and Directors' Remuneration Report
Shareholder waiver of dividends	Page 106 in the Corporate Governance Report

Property
Substantially all of our properties are held freehold, free of material encumbrances and are fit for their purpose. For more information please refer to Note 7 to the Group Financial Statements on page 167.

Tax information for shareholders
Taxation for US persons
The following summary of material UK and US federal income tax consequences of ownership of Ordinary Shares or ADRs held as capital assets by the US holders described below is based on current UK and US federal income tax law, including the US/UK double taxation convention relating to income and capital gains, which entered into force on 31 March 2003 (the Convention). This summary does not describe all of the tax consequences that may be relevant in light of the US holders' particular circumstances and tax consequences applicable to US holders subject to special rules (such as certain financial institutions, entities treated as partnerships for US federal income tax purposes, persons whose functional currency for US federal income tax purposes is not the US dollar, tax-exempt entities, persons that own directly, indirectly or constructively ADRs or Ordinary Shares representing 10% or more of our voting power or value, persons subject to alternative minimum tax, persons subject to the Medicare contribution tax on 'net investment income', or persons holding Ordinary Shares or ADRs in connection with a trade or business conducted outside of the US). US holders are urged to consult their tax advisers regarding the UK and US federal income tax consequences of the ownership and disposition of Ordinary Shares or ADRs in their particular circumstances.

This summary is based in part on representations of Citibank as depositary for ADRs and assumes that each obligation in the deposit agreement among the Company and the depositary and the holders from time to time of ADRs and any related agreements will be performed in accordance with its terms. The US Treasury has expressed concerns that parties to whom American depositary shares are released before shares are delivered to the depositary (pre-release), or intermediaries in the chain of ownership between holders and the issuer of the security underlying the American depositary shares, may be taking actions that are inconsistent with the claiming, by US holders of American depositary shares, of foreign tax credits for US federal income tax purposes. Such actions would also be inconsistent with the claiming of the reduced tax rates, described below, applicable to dividends received by certain non-corporate US holders. Accordingly, the availability of the reduced tax rates for dividends received by certain non-corporate US holders could be affected by actions that may be taken by parties to whom ADRs are pre-released.

For the purposes of this summary, the term 'US holder' means a beneficial owner of Ordinary Shares or ADRs that is, for US federal income tax purposes, a citizen or resident of the US, a corporation (or other entity taxable as a corporation) created or organised in or under the laws of the US, any state in the US or the District of Columbia, or an estate or trust, the income of which is subject to US federal income taxation regardless of its source.

This summary assumes that we are not, and will not become, a passive foreign investment company, as discussed below.

UK and US income taxation of dividends
The UK does not currently impose a withholding tax on dividends paid by a UK company, such as the Company.

For US federal income tax purposes, distributions paid by the Company to a US holder are included in gross income as foreign source ordinary dividend income to the extent paid out of the Company's current or accumulated earnings and profits, calculated in accordance with US federal income tax principles. The Company does not maintain calculations of its earnings and profits under US federal income tax principles and so it is expected that distributions generally will be reported to US holders as dividends. The amount of the dividend will be the US dollar amount received by the depositary for US holders of ADRs (or, in the case of Ordinary Shares, the US dollar value of the foreign currency payment, determined at the spot rate of the relevant foreign currency on the date the dividend is received by the US holders, regardless of whether the dividend is converted into US dollars), and it will not be eligible for the dividends received deduction generally available to US corporations. If the dividend is converted into US dollars on the date of receipt, US holders of Ordinary Shares generally should not be required to recognise foreign currency gains or losses in respect of the dividend income. They may have foreign currency gain or loss (taxable at the rates applicable to ordinary income) if the amount of such dividend is converted into US dollars after the date of its receipt.

Subject to applicable limitations and the discussion above regarding concerns expressed by the US Treasury, dividends received by certain non-corporate US holders of Ordinary Shares or ADRs may be taxable at favourable US federal income tax rates. US holders should consult their own tax advisers to determine whether they are subject to any special rules which may limit their ability to be taxed at these favourable rates.

Taxation on capital gains
Under present English law, individuals who are neither resident nor ordinarily resident in the UK, and companies which are not resident in the UK, will not be liable for UK tax on capital gains made on the disposal of their Ordinary Shares or ADRs, unless such Ordinary Shares or ADRs are held in connection with a trade, profession or vocation carried on in the UK through a branch or agency or other permanent establishment.

A US holder will generally recognise US source capital gains or losses for US federal income tax purposes on the sale or exchange of Ordinary Shares or ADRs in an amount equal to the difference between the US dollar amount realised and such holder's US dollar tax basis in the Ordinary Shares or ADRs. US holders should consult their own tax advisers about the treatment of capital gains, which may be taxed at lower rates than ordinary income for non-corporate US holders and capital losses, the deductibility of which may be subject to limitations.

Passive Foreign Investment Company (PFIC) rules

We believe that we were not a PFIC for US federal income tax purposes for the year ended 31 December 2018. However, since PFIC status depends on the composition of our income and assets, and the market value of our assets (including, among others, less than 25% owned equity investments), from time to time, there can be no assurance that we will not be considered a PFIC for any taxable year. If we were treated as a PFIC for any taxable year during which Ordinary Shares or ADRs were held, certain adverse tax consequences could apply to US holders.

Information reporting and backup withholding

Payments of dividends and sales proceeds that are made within the US or through certain US-related financial intermediaries may be subject to information reporting and backup withholding, unless: (i) the US holder is a corporation or other exempt recipient; or (ii) in the case of backup withholding, the US holder provides a correct taxpayer identification number and certifies that it is not subject to backup withholding. The amount of any backup withholding from a payment to a US holder will be allowed as a credit against the holder's US federal income tax liability and may entitle the holder to a refund, provided that the required information is timely supplied to the US Internal Revenue Service (IRS).

Certain US holders who are individuals (or certain specified entities), may be required to report information relating to securities issued by non-US persons (or foreign accounts through which the securities are held), generally on IRS Form 8938, subject to certain exceptions (including an exception for securities held in accounts maintained by US financial institutions). US holders should consult their tax advisers regarding their reporting obligations with respect to the Ordinary Shares or ADRs.

UK inheritance tax

Under the current Double Taxation (Estates) Convention (the Estate Tax Convention) between the US and the UK, Ordinary Shares or ADRs held by an individual shareholder who is domiciled for the purposes of the Estate Tax Convention in the US, and is not for the purposes of the Estate Tax Convention a national of the UK, will generally not be subject to UK inheritance tax on the individual's death or on a chargeable gift of the Ordinary Shares or ADRs during the individual's lifetime, provided that any applicable US federal gift or estate tax liability is paid, unless the Ordinary Shares or ADRs are part of the business property of a permanent establishment of the individual in the UK or, in the case of a shareholder who performs independent personal services, pertain to a fixed base situated in the UK. Where the Ordinary Shares or ADRs have been placed in trust by a settlor who, at the time of settlement, was a US domiciled shareholder, the Ordinary Shares or ADRs will generally not be subject to UK inheritance tax unless the settlor, at the time of settlement, was a UK national, or the Ordinary Shares or ADRs are part of the business property of a permanent establishment of the individual in the UK or, in the case of a shareholder who performs independent personal services, pertain to a fixed base situated in the UK. In the exceptional case where the Ordinary Shares or ADRs are subject to both UK inheritance tax and US federal gift or estate tax, the Estate Tax Convention generally provides for double taxation to be relieved by means of credit relief.

UK stamp duty reserve tax and stamp duty

A charge to UK stamp duty or UK stamp duty reserve tax (SDRT) may arise on the deposit of Ordinary Shares in connection with the creation of ADRs. The rate of stamp duty or SDRT will generally be 1.5% of the value of the consideration or, in some circumstances, the value of the Ordinary Shares. There is no 1.5% SDRT charge on the issue of Ordinary Shares (or, where it is integral to the raising of new capital, the transfer of Ordinary Shares) into the ADR arrangement.

No UK stamp duty will be payable on the acquisition or transfer of existing ADRs provided that any instrument of transfer or written agreement to transfer is executed outside the UK and remains at all times outside the UK. An agreement for the transfer of ADRs will not give rise to a liability for SDRT.

A transfer of, or an agreement to, transfer Ordinary Shares will generally be subject to UK stamp duty or SDRT at 0.5% of the amount or value of any consideration, provided, in the case of stamp duty, it is rounded up to the nearest £5.

Transfers of Ordinary Shares into CREST will generally not be subject to stamp duty or SDRT, unless such a transfer is made for a consideration in money or money's worth, in which case a liability to SDRT will arise, usually at the rate of 0.5% of the value of the consideration. Paperless transfers of Ordinary Shares within CREST are generally liable to SDRT at the rate of 0.5% of the value of the consideration. CREST is obliged to collect SDRT from the purchaser on relevant transactions settled within the system.

Exchange controls and other limitations affecting security holders

There are no governmental laws, decrees or regulations in the UK restricting the import or export of capital or affecting the remittance of dividends, interest or other payments to non-resident holders of Ordinary Shares or ADRs.

There are no limitations under English law or the Articles on the right of non-resident or foreign owners to be the registered holders of, or to exercise voting rights in relation to, Ordinary Shares or ADRs or to be registered holders of notes or debentures of the Company or its wholly-owned subsidiary, Zeneca Wilmington Inc.

Exchange rates

The following information relating to average and spot exchange rates used by AstraZeneca is provided for convenience:

	SEK/USD	USD/GBP
Average rates (statement of comprehensive income, statement of cash flows)		
2018	**8.6419**	**1.3405**
2017	8.5835	1.2835
2016	8.5286	1.3673
End of year spot rates (statement of financial position)		
2018	**8.9537**	**1.2743**
2017	8.2467	1.3468
2016	9.1162	1.2272

Trade Marks

AstraZeneca, the AstraZeneca logotype, and the AstraZeneca symbol are all trade marks of the Group.

The following brand names which appear in italics in this Annual Report are trade marks of the Group:

Trade mark			
Arimidex	*Diprivan*[2]	*Marcaine*[2]	*Seloken*
Atacand[1]	*Duzallo*	*Movantik*	*Seroquel*
Atacand HCT	*EMLA*[2]	*Moventig*	*Seroquel XR*
Atacand Plus[1]	*Farxiga*	*Naropin*[2]	*Symbicort*
BCise	*Fasenra*	*Nexium*	*Symbicort SMART*
Bevespi Aerosphere	*Faslodex*	*Onglyza*	*Symbicort Turbuhaler*
Brilinta	*Fluenz*	*Plendil*	*Symlin*
Brilique	*FluMist*	*Pressair*	*Synagis*[5]
Bydureon	*Forxiga*	*Prilosec*	*Tagrisso*
Byetta	*Genuair*	*Provisacor*	*Toprol-XL*
Calquence	*Imdur*[3]	*Pulmicort*	*Turbuhaler*
Carbocaine[2]	*Imfinzi*	*Pulmicort Flexhaler*	*Vimovo*[6]
Casodex	*Iressa*	*Pulmicort Respules*	*Xigduo*
Citanest[2]	*Kombiglyze*	*Pulmicort Turbuhaler*	*Xylocaine*[2]
Cosudex	*Komboglyze*	*Qtern*	*Zavicefta*[7]
Crestor	*Losec*	*Respules*	*Zoladex*
Daliresp	*Lokelma*	*Rhinocort*[4]	*Zomig*[8]
Daxas	*Lynparza*	*Rhinocort Aqua*[4]	*Zurampic*

1 AstraZeneca divested these trade marks in Europe to Cheplapharm effective 28 September 2018.
2 AstraZeneca divested these trade marks to Aspen group effective 1 November 2017.
3 AstraZeneca assigned this trade mark to Everest Future Limited effective 1 May 2016.
4 AstraZeneca assigned *Rhinocort* and *Rhinocort Aqua* to Cilag outside the US effective 5 December 2016.
5 AstraZeneca owns this trade mark in the US only. AbbVie owns it in the rest of the world.
6 AstraZeneca divested the global rights (excluding the US and Japan) for this trade mark to Grünenthal, effective 3 December 2018.
7 AstraZeneca assigned this trade mark to Pfizer Inc. effective 23 December 2016.
8 AstraZeneca assigned the rights to this trade mark outside Japan to Grünenthal effective 7 June 2017. In Japan, AstraZeneca divested this product to Sawai Pharmaceutical effective 3 October 2017.

The following brand names which appear in italics in this Annual Report are trade marks licensed to the Group by the entities set out below:

Trade mark	Licensor or Owner
Anticalin	Pieris AG
Duaklir	Almirall, S.A.
Eklira	Almirall, S.A.
Epanova	Chrysalis Pharma AG
Fluimucil	Zambon S.p.A.
Linzess	Ironwood
Lumoxiti	Innate Pharma
Tudorza	Almirall, S.A.

The following brand names which appear in italics throughout this Annual Report are not owned by or licensed to the Group and are owned by the entities set out below:

Trade mark	Owner
Imbruvica	Depending on geography, the trade mark is owned by Pharmacyclics, Inc., Johnson & Johnson or Janssen Pharmaceutica NV.
Keytruda	MSD
messenger RNA Therapeutics	Moderna

Glossary

Market definitions

Region	Country				
US	US				
Europe	Albania*	Czech Republic	Hungary	Luxembourg*	Serbia and Montenegro*
	Austria	Denmark	Iceland*	Malta*	Slovakia*
	Belgium	Estonia*	Ireland	Netherlands	Slovenia*
	Bosnia and Herzegovina*	Finland	Israel*	Norway	Spain
	Bulgaria	France	Italy	Poland	Sweden
	Croatia	Germany	Latvia*	Portugal*	Switzerland
	Cyprus*	Greece	Lithuania*	Romania	UK
Established ROW	Australia	Canada	Japan	New Zealand	
Emerging Markets	Algeria	Costa Rica	Iraq*	Pakistan*	Syria*
	Argentina	Cuba*	Jamaica*	Palestine*	Taiwan
	Aruba*	Dominican Republic*	Jordan*	Panama	Thailand
	Bahamas*	Ecuador*	Kazakhstan	Peru	Trinidad and Tobago*
	Bahrain*	Egypt	Kuwait*	Philippines	Tunisia*
	Barbados*	El Salvador	Lebanon*	Qatar*	Turkey
	Belarus*	Georgia*	Libya*	Russia	Ukraine*
	Belize*	Guatemala	Malaysia	Saudi Arabia	United Arab Emirates
	Bermuda*	Honduras	Mexico	Singapore	Uruguay*
	Brazil	Hong Kong	Morocco*	South Africa	Venezuela*
	Chile	India	Nicaragua	South Korea	Vietnam
	China	Indonesia	Oman*	Sri Lanka*	Yemen*
	Colombia	Iran*	Other Africa*	Sudan*	

* IQVIA, IQVIA Midas Quantum Q3 2018 data is not available or AstraZeneca does not subscribe for IQVIA quarterly data for these countries.

The above table is not an exhaustive list of all the countries in which AstraZeneca operates, and excludes countries with revenue in 2018 of less than $1 million.

Established Markets means US, Europe and Established ROW.

North America means US and Canada.

Other Established ROW means Australia and New Zealand.

Other Emerging Markets means all Emerging Markets except China.

Other Africa includes Angola, Botswana, Ethiopia, Ghana, Kenya, Mauritius, Mozambique, Namibia, Nigeria, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe.

Asia Area comprises India, Indonesia, Malaysia, Philippines, Singapore, South Korea, Sri Lanka, Taiwan, Thailand and Vietnam.

US equivalents

Terms used in this Annual Report	US equivalent or brief description
Accruals	Accrued expenses
Called-up share capital	Issued share capital
Creditors	Liabilities/payables
Debtors	Receivables and prepaid expenses
Earnings	Net income
Employee share schemes	Employee stock benefit plans
Fixed asset investments	Non-current investments
Freehold	Ownership with absolute rights in perpetuity
Loans	Long-term debt
Prepayments	Prepaid expenses
Profit	Income
Share premium account	Additional paid in capital or paid in surplus (not distributable)
Short-term investments	Redeemable securities and short-term deposits

Glossary
continued

The following abbreviations and expressions have the following meanings when used in this Annual Report:

AbbVie – AbbVie Inc.

ACA (Affordable Care Act) – the US Patient Protection and Affordable Care Act which was signed into law on 23 March 2010 as amended by the Health Care and Education Reconciliation Act which was signed into law on 30 March 2010.

Acerta Pharma – Acerta Pharma B.V.

ACS – acute coronary syndromes.

Actavis – Actavis plc.

ADR – an American Depositary Receipt evidencing title to an ADS.

ADS – an American Depositary Share representing half an underlying Ordinary Share.

Aegerion – Aegerion Pharmaceuticals, Inc.

AGM – an Annual General Meeting of the Company.

AI – artificial intelligence.

Almirall – Almirall, S.A.

Amgen – Amgen, Inc.

Amplimmune – Amplimmune, Inc.

ANDA – an abbreviated new drug application, which is a marketing approval application for a generic drug submitted to the FDA.

Annual Report – this Annual Report and Form 20-F Information 2018.

API – active pharmaceutical ingredient.

Aralez – Aralez Pharmaceuticals Trading DAC.

Ardea – Ardea Biosciences, Inc.

Articles – the Articles of Association of the Company.

Aspen – Aspen Global Incorporated.

Astellas – Astellas Pharma Inc.

Astra – Astra AB, being the company with whom the Company merged in 1999.

AstraZeneca – the Company and its subsidiaries.

AstraZeneca HealthCare Foundation – a Delaware, US not-for-profit corporation and a 501(c)(3) entity, separate from AstraZeneca Pharmaceuticals, organised for charitable purposes including to promote public awareness and education of healthcare issues and support eligible nonprofit organisations in alignment with its mission. The Foundation has received $30 million in contributions to date from AstraZeneca to support the *Connections for Cardiovascular Health*℠ programme.

ATM – Ataxia telangiectasia mutated.

Avillion – Avillion LLP.

AZIP – AstraZeneca Investment Plan.

BACE – beta secretase cleaving enzyme.

biologic(s) – a class of drugs that are produced in living cells.

biosimilars – a copy of a biologic that is sufficiently similar to meet regulatory requirements.

BMS – Bristol-Myers Squibb Company.

Board – the Board of Directors of the Company.

Bureau Veritas – Bureau Veritas UK Limited.

CDP – a not-for-profit that runs the global disclosure system for investors, companies, cities, states and regions to manage their environmental impacts.

Celgene – Celgene International Sàrl/Celgene Corporation.

CEO – the Chief Executive Officer of the Company.

CER – constant exchange rates.

CFO – the Chief Financial Officer of the Company.

Cheplapharm – Cheplapharm Arzneimittel GmbH.

CHMP – the Committee for Medicinal Products for Human Use.

Cilag – Cilag GmbH International.

Circassia – Circassia Pharmaceuticals plc.

CIS – Commonwealth of Independent States.

CKD – Chronic kidney disease.

CMS – China Medical System Holdings Ltd.

Code of Ethics – the Group's Code of Ethics.

Company or Parent Company – AstraZeneca PLC (formerly Zeneca Group PLC (Zeneca)).

COPD – chronic obstructive pulmonary diseases.

Covis – Covis Pharma B.V.

CREST – UK-based securities settlement system.

CRL – Complete Response Letter.

CROs – contract research organisations.

CRUK – Cancer Research UK.

CV – cardiovascular.

CVRM – Cardiovascular, Renal and Metabolism.

Daiichi Sankyo – Daiichi Sankyo, Inc.

Definiens – Definiens AG.

Director – a director of the Company.

DJSI – Dow Jones Sustainability Index.

DOJ – the United States Department of Justice.

DTR – UK Disclosure Guidance and Transparency Rules.

earnings per share (EPS) – profit for the year after tax and non-controlling interests, divided by the weighted average number of Ordinary Shares in issue during the year.

EBITDA – 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.

EC – European Commission.

EFPIA – European Federation of Pharmaceutical Industries and Associations.

EGFR – epidermal growth factor receptor.

EMA – European Medicines Agency.

Entasis – Entasis Therapeutics Ltd and Entasis Therapeutics Inc.

EPO – European Patent Office.

ERK – extracellular signal-regulated kinases.

ESMO – European Society for Medical Oncology.

ESPC – Early Stage Product Committee.

ESRD – end-stage renal disease.

EVP – Executive Vice-President.

EU – the European Union.

EU 5 – European Union Five (France, Germany, Italy, Spain and the UK).

FDA – the US Food and Drug Administration, which is part of the US Department of Health and Human Services Agency, which is the regulatory authority for all pharmaceuticals (including biologics and vaccines) and medical devices in the US.

FDC – fixed-dose combination.

FibroGen – FibroGen, Inc.

FRC – Financial Reporting Council.

GAAP – Generally Accepted Accounting Principles.

GDPR – General Data Protection Regulation.

GINA – Global Initiative for Asthma.

GQCE – Generics Quality Consistency Evaluation.

Gilead – Gilead Sciences, Inc.

GMD – Global Medicines Development.

GPPS – Global Product and Portfolio Strategy.

gross margin – the margin, as a percentage, by which sales exceed the cost of sales, calculated by dividing the difference between the two by the sales figure.

Group – AstraZeneca PLC and its subsidiaries.

Grünenthal – Grünenthal Group.

GSK – GlaxoSmithKline plc.

HF – heart failure.

HFA – hydrofluoroalkane.

HHA – Healthy Heart Africa programme.

HNSCC – head and neck squamous cell carcinoma.

HR – human resources.

HTA – health technology assessment.

IA – the Group's Internal Audit Services function.

IAS – International Accounting Standards.

IASB – International Accounting Standards Board.

ICS – inhaled corticosteroid.

IFPMA – International Federation of Pharmaceutical Manufacturers and Associations.

IFRS – International Financial Reporting Standards or International Financial Reporting Standard, as the context requires.

IMED – Innovative Medicines and Early Development.

Innate Pharma – Innate Pharma S.A.

IO – immuno-oncology.

IP – intellectual property.

IQVIA – IQVIA Solutions HQ Limited. For more information, see page 244.

Ironwood – Ironwood Pharmaceuticals, Inc.

IS – information services.

ISAs – International Standards on Auditing.

IT – information technology.

Johnson & Johnson – Johnson & Johnson.

KPI – key performance indicator.

krona or SEK – references to the currency of Sweden.

Kyowa Hakko Kirin – Kyowa Hakko Kirin Co., Ltd.

LABA – long-acting beta2-agonist.

LAMA – long-acting muscarinic antagonist.

LCM projects – significant life-cycle management projects (as determined by potential revenue generation), or line extensions.

Lean – means enhancing value for customers with fewer resources.

LEO Pharma – LEO Pharma A/S.

Lilly – Eli Lilly and Company.

LSPC – Late Stage Product Committee.

LTI – long-term incentive, in the context of share plan remuneration arrangements.

Luye Pharma – Luye Pharma Group.

MAA – a marketing authorisation application, which is an application for authorisation to place medical products on the market. This is a specific term used in the EU and European Economic Area markets.

mAb – monoclonal antibody, a biologic that is specific, that is, it binds to and attacks one particular antigen.

major market – US, EU, Japan (JP) and China (CN).

MAT – moving annual total.

MedImmune – MedImmune, LLC (formerly MedImmune, Inc.).

MEK – part of the mitogen-activated protein kinase (MAPK) pathway.

MI – myocardial infarction.

Moderna – Moderna Therapeutics, Inc.

MSD – Merck & Co., Inc., which is known as Merck in the US and Canada and MSD in other territories.

Nasdaq Stockholm – previously the Stockholm Stock Exchange.

NCD – non-communicable disease.

NDA – a new drug application to the FDA for approval to market a new medicine in the US.

New Medicines – *Tagrisso*, *Imfinzi*, *Lynparza*, *Calquence*, *Lumoxiti*, *Farxiga*, *Brilinta*, *Lokelma*, *Bevespi* and *Fasenra*.

NME – new molecular entity.

NMPA – National Medical Products Administration, formerly the China Food and Drug Administration (CFDA).

Novartis – Novartis Pharma AG.

Novo Nordisk – Novo Nordisk A/S.

NSAID – a non-steroidal anti-inflammatory drug.

NSCLC – non-small cell lung cancer.

NYSE – the New York Stock Exchange.

n/m – not meaningful.

OECD – the Organisation for Economic Co-operation and Development.

OIC – opioid-induced constipation.

Omthera – Omthera Pharmaceuticals, Inc.

operating profit – sales, less cost of sales, less operating costs, plus operating income.

Ordinary Share – an ordinary share of $0.25 each in the share capital of the Company.

Orphan Drug – a drug which has been approved for use in a relatively low-incidence indication (an orphan indication) and has been rewarded with a period of market exclusivity; the period of exclusivity and the available orphan indications vary between markets.

OTC – over-the-counter.

Paediatric Exclusivity – in the US, a six-month period of exclusivity to market a drug which is awarded by the FDA in return for certain paediatric clinical studies using that drug. This six-month period runs from the date of relevant patent expiry. Analogous provisions are available in certain other territories (such as European Supplementary Protection Certificate (SPC) paediatric extensions).

PARP – an oral poly ADP-ribose polymerase.

PD-L1 – an anti-programmed death-ligand 1.

Pearl Therapeutics – Pearl Therapeutics, Inc.

Pfizer – Pfizer, Inc.

PFS – progression-free survival. The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse.

PhRMA – Pharmaceutical Research and Manufacturers of America.

Phase I – the phase of clinical research where a new drug or treatment is tested in small groups of people (20 to 80) to check that the drug can achieve appropriate concentrations in the body, determine a safe dosage range and identify side effects. This phase includes healthy volunteer studies.

Phase II – the phase of clinical research which includes the controlled clinical activities conducted to evaluate the effectiveness of the drug in patients with the disease under study and to begin to determine the safety profile of the drug. Phase II studies are typically conducted in small- or medium-sized groups of patients and can be divided into Phase IIa studies, which tend to be designed to assess dosing requirements, and Phase IIb studies, which tend to assess safety and efficacy.

Phase III – the phase of clinical research which is performed to gather additional information about effectiveness and safety of the drug, often in a comparative setting, to evaluate the overall benefit/risk profile of the drug. Phase III studies usually include between several hundred and several thousand patients.

Glossary
continued

PHC – personalised healthcare.

Pieris Pharmaceuticals – Pieris Pharmaceuticals, Inc.

PMDA – Pharmaceuticals and Medical Devices Agency of Japan.

pMDI – pressurised metered-dose inhaler.

pound sterling, £, GBP or pence – references to the currency of the UK.

Pozen – POZEN, Inc.

primary care – general healthcare provided by physicians who ordinarily have first contact with patients and who may have continuing care for them.

Proof of Concept – data demonstrating that a candidate drug results in a clinical change on an acceptable endpoint or surrogate in patients with the disease.

PSP – AstraZeneca Performance Share Plan.

PTE – Patent Term Extension, an extension of up to five years in the term of a US patent relating to a drug which compensates for delays in marketing resulting from the need to obtain FDA approval. The analogous right in the EU is an SPC.

R&D – research and development.

Recordati – Recordati S.p.A.

Redeemable Preference Share – a redeemable preference share of £1 each in the share capital of the Company.

Regulatory Data Protection (RDP) – see Intellectual Property from page 35.

Regulatory Exclusivity – any of the IP rights arising from generation of clinical data and includes Regulatory Data Protection, Paediatric Exclusivity and Orphan Drug status.

RNA – ribonucleic acid.

Roche – F. Hoffmann-La Roche AG.

ROW – rest of world.

RSV – respiratory syncytial virus.

Sanofi – SANOFI S.A./Sanofi Pasteur, Inc.

Sarbanes-Oxley Act – the US Sarbanes-Oxley Act of 2002.

SDRT – UK stamp duty reserve tax.

SEC – the US Securities and Exchange Commission, the governmental agency that regulates the US securities industry and stock markets.

Seroquel – *Seroquel* IR and *Seroquel XR*.

SET – Senior Executive Team.

SG&A costs – selling, general and administrative costs.

SGLT-2 – sodium-glucose co-transporter 2.

SHE – Safety, Health and Environment.

Shionogi – Shionogi & Co. Ltd.

Shire – Shire plc.

SLE – systemic lupus erythematosus.

sNDA – supplemental New Drug Application.

Sobi – Swedish Orphan Biovitrum AB.

SPC – supplementary protection certificate.

specialty care – specific healthcare provided by medical specialists who do not generally have first contact with patients.

Spirogen – Spirogen Sàrl.

SoC – standard of care. Treatment that is accepted by medical experts as a proper treatment for a certain type of disease and that is widely used by healthcare professionals.

Takeda – Takeda Pharmaceutical Company Limited.

TerSera – TerSera Therapeutics LLC.

Teva – Teva Pharmaceuticals USA, Inc.

Total Revenue – the sum of Product Sales and Externalisation Revenue.

TSR – total shareholder return, being the total return on a share over a period of time, including dividends reinvested.

UK – United Kingdom of Great Britain and Northern Ireland.

UK Corporate Governance Code – the UK Corporate Governance Code published by the FRC in April 2016 that sets out standards of good practice in corporate governance for the UK.

US – United States of America.

US dollar, US$, USD or $ – references to the currency of the US.

Valeant – Valeant Holdings Ireland/Valeant Pharmaceutical International, Inc.

Viela Bio – Viela Bio, Inc.

WHO – World Health Organization, the United Nations' specialised agency for health.

YHP – Young Health Programme.

Zambon – Zambon S.p.A.

ZS Pharma – ZS Pharma, Inc.

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Important information for readers of this Annual Report

Cautionary statement regarding forward-looking statements

The purpose of this Annual Report is to provide information to the members of the Company. The Company and its Directors, employees, agents and advisers do not accept or assume responsibility to any other person to whom this Annual Report is shown or into whose hands it may come and any such responsibility or liability is expressly disclaimed. In order, among other things, to utilise the 'safe harbour' provisions of the US Private Securities Litigation Reform Act of 1995 and the UK Companies Act 2006, we are providing the following cautionary statement: This Annual Report contains certain forward-looking statements with respect to the operations, performance and financial condition of the Group, including, among other things, statements about expected revenues, margins, earnings per share or other financial or other measures. Forward-looking statements are statements relating to the future which are based on information available at the time such statements are made, including information relating to risks and uncertainties. Although we believe that the forward-looking statements in this Annual Report are based on reasonable assumptions, the matters discussed in the forward-looking statements may be influenced by factors that could cause actual outcomes and results to be materially different from those expressed or implied by these statements. The forward-looking statements reflect knowledge and information available at the date of the preparation of this Annual Report and the Company undertakes no obligation to update these forward-looking statements. We identify the forward-looking statements by using the words 'anticipates', 'believes', 'expects', 'intends' and similar expressions in such statements. Important factors that could cause actual results to differ materially from those contained in forward-looking statements, certain of which are beyond our control, include, among other things, those factors identified in the Risk section from page 220 of this Annual Report. Nothing in this Annual Report should be construed as a profit forecast.

Inclusion of Reported performance, Core financial measures and constant exchange rate growth rates

AstraZeneca's determination of non-GAAP measures together with our presentation of them within our financial information may differ from similarly titled non-GAAP measures of other companies.

Statements of competitive position, growth rates and sales

In this Annual Report, except as otherwise stated, market information regarding the position of our business or products relative to its or their competition is based upon published statistical sales data for the 12 months ended 30 September 2018 obtained from IQVIA, a leading supplier of statistical data to the pharmaceutical industry. Unless otherwise noted, for the US, dispensed new or total prescription data and audited sales data are taken, respectively, from IQVIA National Prescription Audit and IQVIA National Sales Perspectives for the 12 months ended 31 December 2018; such data is not adjusted for Medicaid and similar rebates. Except as otherwise stated, these market share and industry data from IQVIA have been derived by comparing our sales revenue with competitors' and total market sales revenues for that period, and except as otherwise stated, growth rates are given at CER. For the purposes of this Annual Report, unless otherwise stated, references to the world pharmaceutical market or similar phrases are to the 52 countries contained in the IQVIA database, which amounted to approximately 88% (in value) of the countries audited by IQVIA.

AstraZeneca websites

Information on or accessible through our websites, including www.astrazeneca.com, www.astrazenecaclinicaltrials.com and www.medimmune.com, does not form part of and is not incorporated into this Annual Report.

External/third-party websites

Information on or accessible through any third-party or external website does not form part of and is not incorporated into this Annual Report.

Figures

Figures in parentheses in tables and in the Financial Statements are used to represent negative numbers.

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FSC
www.fsc.org
MIX
Paper from responsible sources
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Registered office and corporate headquarters
AstraZeneca PLC
1 Francis Crick Avenue
Cambridge Biomedical Campus
Cambridge CB2 0AA
UK
Tel: +44 (0)20 3749 5000

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