White Paper

Citeline
Pharma Intelligence

30th Anniversary of Pharma R&D Annual Review

Pharma R&D Annual Review 2022 Supplement:

New Active Substances Launched During 2021

Discover more at:
pages.pharmaintelligence.informa.com/rdreview#NAS

Introduction

Following on from our review of trends in the current pharmaceutical R&D pipeline (download the report for free), this supplement takes a look at the industry's success stories of 2021 – the drugs which were launched onto the market for the first time during the year. Our survey focuses exclusively on new active substances (NASs): new chemical or biological entities where the active ingredient had received no prior approval for human use. This would also include vaccines with novel antigenic components. As such, this list represents a subset of all the first launches which Pharmaprojects reported during 2021, and excludes an additional 75 first drug launches of reformulated or non-NAS moieties, biosimilars, and imaging agents. So, to continue with our travel-based theme this year, these are drugs which remembered their passports, tickets, and vaccine certificates, boarded the plane for their flight through clinical development, touched down safely, and have now successfully completed their journey and arrived at their chosen destination.

Travel was one of the pleasures in life which we had previously taken for granted that was most affected by the COVID-19 pandemic over the past two years. Whereas usually, one could board a plane at the drop of a hat and be in foreign climes by teatime, for much of 2020 and 2021, international travel was completely out of the question. Indeed, during lockdowns, in the UK at least, we were only permitted to leave our homes for essential food buying or our once-daily permitted bout of exercise. As our worlds essentially shrank to the size of our living rooms, somehow, drugs continued on their journeys through research and development.

In the first part of this year's Pharma R&D Review, we saw how little the pharma industry seems to have been perturbed by arguably the biggest global crisis of modern times. Pipelines continued to grow, new companies sprang up, and, after an initial readjustment, clinical trials continued. At the same time, an unprecedented effort was diverted to tackling a completely new disease with extreme urgency. Having responded so quickly to altered circumstances through 2020, it seems to have largely been business as usual for pharma in 2021. But, with a record-breaking and expectation-confounding number of new drugs launched during the first year of the pandemic, surely the delivery of new medicines onto the market must have taken some kind of hit in 2021? In this report, we will examine in detail the numbers, types, and novelty of the drugs which, in the last calendar year, successfully completed their development journeys, and are now sitting back and relaxing on their deckchairs, sipping a piña colada and basking in the sunshine of success. Let's start by taking in the view of the full list of NASs which were launched across the year just passed.

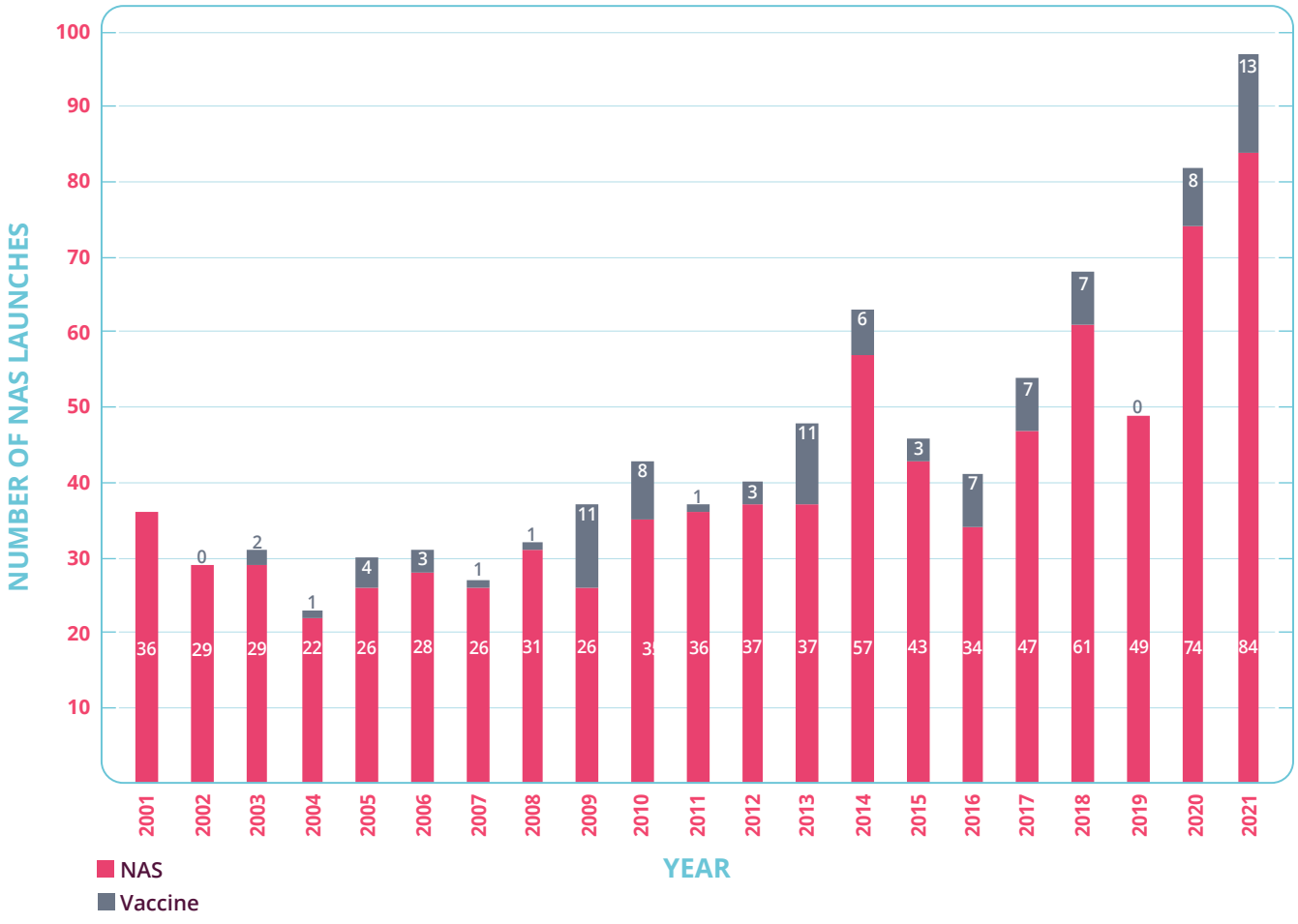
97 New Active Substance Launches

Pharma defies the pandemic to go supersonic

Once again, the pharma industry has confounded its critics and surpassed expectations. After setting a new record for drug launches in 2020 with 82 NASs, somehow, that record has been smashed yet again. 2021 saw 97 NASs across 95 new products (two launches were combination products containing two NASs apiece). So, despite all the disruption to trials, supply chains, and launch plans; despite all the sudden diversions of resources which the pandemic precipitated; despite everything, pharma landed a record number of its travellers in the new territory. A sound barrier smashing result, to be sure.

As Figure 1 shows, rather than being hampered by COVID, the past two years were by some distance the best ever, with 2021's tally being almost double that seen only two years earlier. Indeed, barring a couple of wobbles, it's pretty clear that the overall trend is soaring inexorably upwards. As usual, we must caveat the data by noting that segmenting NAS launches by calendar year is a somewhat arbitrary way of counting NAS success, since a few just missing

FIGURE 1:
Number of NAS launches by year, 2001–21



Source: Pharmaprojects®, February 2022

the end of one year and spilling over into the next might depress the first year's figures while boosting the second's. But that certainly didn't happen from 2020 to 2021. Might we be heading for pharma breaching the three-figure barrier in annual delivery of new drugs sometime soon?

It's undoubtedly the case that COVID has stimulated, rather than hampered, this figure; of the 13 vaccines included in the total this year, 11 are against the novel coronavirus. But it is encouraging to see that the non-vaccine number of NASs is also overtaking last year's total in the fast lane. Stripping out the vaccine figures, we can take a better look at the overall direction of travel. The mean number of non-vaccine NASs for the past five years (2017–21) is now 63.0, up from the 53.0 five-year figure reported last year. Not only is the rolling average creeping up, it's also opening up more and more road between it and previous five-year means: 41.6 for 2012–16, 30.8 for 2007–11, and 26.8 for 2002–06. In other words, the pharma industry has managed to more than double its mean output over the past decade. In travel terms, it really is going supersonic.

The 2021 NAS Statistics

Unpacking this year's newcomers

With the pharma plane packed to the rafters with excited newcomers venturing out into the wider world for the first time, let's take a look at the full passenger list. After months of careful curation, we can present to you in Table 1 (overleaf) the definitive list of 2021's new active substance launches worldwide. Included in this alphabetical list by INN or equivalent is data on the companies involved, diseases which the drugs are approved for and their mechanisms of action, where the launches first occurred, and indications of novelty and rare disease/orphan drug status. We'll go on to analyse our roster of travellers by each of these measures through the rest of this report. As noted already, there are only 95 rows in the table and 95 products, but because two products are combination drugs which contain two NASs, our overall NAS count comes in at 97.

TABLE 1:
New active substance launches, 2021

GENERIC DRUG NAME	TRADE NAME	COMPANY	DRUG DISEASE	MECHANISM OF ACTION	DRUG COUNTRY	MONTH OF LAUNCH	FIRST-IN-CLASS?	RARE DISEASE?	ORPHAN DRUG STATUS?
aducanumab	Aduhelm	Biogen/Eisai	Alzheimer's disease	Beta amyloid protein antagonist	USA	July	Y	N	N
ainuovurine	Ai bang de	Kainos Medicine/ Jiangsu Aidea Pharmaceutical	HIV/AIDS infection	Non-nucleoside reverse transcriptase inhinitor	China	September	N	N	N
allogeneic processed thymus tissue-agdc	Rethymic	Enzyvant Sciences/ Sumitomo Danippon Pharma	DiGeorge syndrome	Not applicable	USA	November	N	Y	Y
amivantamab	Rybrevant	Janssen (Johnson & Johnson)	Non-small cell lung cancer	EGFR antagonist//MET tyrosine kinase inhibitor	USA	June	N	N	N
anamorelin hydrochloride	Adlumiz	Ono Pharmaceutical	Anorexia/cachexia	Growth hormone secretagogue receptor agonist	Japan	March	N	N	N
anifrolumab	Saphnelo	AstraZeneca	Systemic lupus erythematosus	Interferon (type I) receptor antagonist	Japan	November	Y	N	N
asciminib	Scemblix	Novartis	Chronic myelogenous leukaemia	Bcr-Abl inhibitor	USA	October	N	Y	Y
atogepant	Qulipta	AbbVie	Migraine prophylaxis	Calcitonin receptor-like receptor antagonist	USA	October	N	N	N
avacopan	Tavneos	ChemoCentryx	Vasculitis/ Microscopic polyangiitis	C5a inhibitor	USA	October	Y	Y	Y
avalglucosidase alfa	Nexviazyme	Sanofi	Pompe's disease	Alpha glucosidase stimulant	USA	August	N	Y	Y
belumosudil	Rezurock	Kadman Holdings	Graft-versus-host disease	Rho-associated kinase 2 inhibitor	USA	August	N	Y	Y
belzutifan	Welireg	Merck & Co	Renal and pancreatic neuroendocrine cancers and Haemangioblastioma in Von Hippel-Lindau disease	Hypoxia-inducible factor 2 alpha antagonist	USA	September	Y	Y	Y
bencycloquidium bromide	BiLiTing	Yingu Pharmaceutical	Allegric rhinitis	Muscarinic M3/M1 antagonist	China	September	N	N	N
bimekizumab	Bimzelx	UCB	Plaque psoriasis	Interleukin 17A/17F^ antagonist	Germany	September	Y	N	N
casimersen	Amondys 45	Sarepta Therapeutics	Duchenne's muscular dystrophy	Dystrophin stimulant	USA	June	N	Y	Y
cetuximab sarotalocan	Akalux	Rakuten Medical	Head and neck cancer	EGFR antagonist	Japan	February	N	N	N
cilgavimab + tixagevimab*	Evusheld	AstraZeneca	COVID-19 infection prophylaxis	Surface glycoprotein (SARS-CoV-2) antagonist	France, Singapore, USA	December	N	N	N
ciprofol	Cyclapofol	Haisco Pharmaceutical	Anaesthesia	GABA A receptor agonist	China	November	N	N	N
clascoterone	Winlevi	Cassiopea/Sun Pharmaceutical Industries	Acne	Androgen receptor antagonist	USA	November	N	N	N
contezolid	YouXiTai	MicuRx	Skin and soft tissue infections	Protein 50S ribosomal subunit inhibitor	China	November	N	N	N
COVID-19 vaccine, Anhui Zhifei Longcom Biopharma	Zifivax	Anhui Zhifel Longcom Biopharma/ Changqing Zhifei Biological	COVID-19 prophylaxis	Immunostimulant	Uzbekistan	April	N	N	N

TABLE 1:
New active substance launches, 2021 *(Cont'd)*

GENERIC DRUG NAME	TRADE NAME	COMPANY	DRUG DISEASE	MECHANISM OF ACTION	DRUG COUNTRY	MONTH OF LAUNCH	FIRST-IN-CLASS?	RARE DISEASE?	ORPHAN DRUG STATUS?
COVID-19 vaccine, AstraZeneca	Covishield	AstraZeneca/ Oxford Biomedica	COVID-19 prophylaxis	Immunostimulant	UK	January	N	N	N
COVID-19 vaccine, Bharat Biotech-1	Covaxin	Bharat Biotech	COVID-19 prophylaxis	Immunostimulant	India	March	N	N	N
COVID-19 vaccine, CanSino Biologics	Convidecia	CanSino Biologics	COVID-19 prophylaxis	Immunostimulant	Pakistan	March	N	N	N
COVID-19 vaccine, CIGB-2	Abdala	CIGB	COVID-19 prophylaxis	Immunostimulant	Vietnam	September	N	N	N
COVID-19 vaccine, Finlay Institute-2	Soberana 2	Finlay Institute	COVID-19 prophylaxis	Immunostimulant	Venezuela	November	N	N	N
COVID-19 vaccine, Johnson & Johnson	Janssen COVID-19 Vaccine	Johnson & Johnson	COVID-19 prophylaxis	Immunostimulant	South Africa	February	N	N	N
COVID-19 vaccine, Medigen Vaccines Biologics Co.	MVC COVID-19 Vaccine	Dynavax Technologies/ Medigen Biotechnology	COVID-19 prophylaxis	Immunostimulant	Taiwan	August	N	N	N
COVID-19 vaccine, Shifa Pharmed	COVIran Barakat	Shifa Pharmed	COVID-19 prophylaxis	Immunostimulant	Iran	June	N	N	N
COVID-19 vaccine, Sinopharm	Sinovac	Wuhan Inst of Biological Sciences/ Sinopharm/ Chinal National Biotec Group	COVID-19 prophylaxis and treatment	Immunostimulant	China	July	N	N	N
COVID-19 vaccine, Vaxine	SpikoGen	Vaxine/ CinnaGen	COVID-19 prophylaxis and treatment	Immunostimulant	Iran	November	N	N	N
cridanimod	Neovir	Pharmasynthez	HBV, HIV and HPV infection	Progesterone receptor agonist; Interferon receptor agonist	Russia	April	N	N	N
disitamab vedotinaide	Aidexi	RemeGen/ Rongchang Pharmaceuticals	Gastrointestinal stomach cancer	Tubulin inhibitor	China	July	N	Y	Y
docaravimab + miromavimab*	Twinrab	Zydus Cadila	Infection, rabies prophylaxis	Immunostimulant	India	March	N	N	N
dostarlimab	Jemperli	GlaxoSmithKline	Endometrial cancer	PD-1 antagonist	USA	May	N	N	N
envafolimab	Enweida	3D Medicines	Colorectal and gastronistelinal stomach cancer	PD-L1 antagonist/Immune checkpoint inhibitor	China	December	N	Y	N
etesevimab		Eli Lilly	COVID-19 treatment and prophylaxis	Surface glycoprotein (SARS-CoV-2) antagonist	Italy	June	N	N	N
evinacumab	Evkeeza	Regeneron	Homozygous familial hypercholesterolaemia	Angiopoietin-like 3 inhibitor	USA	February	Y	Y	Y
finerenone	Kerendia	Bayer	Diabetic nephropathy	Aldosterone antagonist	USA	July	N	N	N
fosdenopterin	Nulibry	BridgeBio Pharma	Molybdenum cofactor deficiency	Molybdenum cofactor stimulant	USA	May	Y	Y	Y
furmonertinib	Ivesa	Allist Pharmaceuticals	Non-small cell lung cancer	EGFR kinase inhibitor	China	March	N	N	N
fuzuloparib	Airuiyi	Jiangsu Hengrui Pharmaceuticals	Epithelial ovarian, fallopian tube and primary peritoneal cancer	Poly ADP ribose polymerase 1/2 inhibitor	China	January	N	Y	N
hetrombopag olamine	HengQu	Jiangsu Hengrui Pharmaceuticals	Primary immune thrombocytopenia	Thrombopoietin agonist	China	September	N	Y	N

TABLE 1:
New active substance launches, 2021 *(Cont'd)*

GENERIC DRUG NAME	TRADE NAME	COMPANY	DRUG DISEASE	MECHANISM OF ACTION	DRUG COUNTRY	MONTH OF LAUNCH	FIRST-IN-CLASS?	RARE DISEASE?	ORPHAN DRUG STATUS?
ibrexafungerp	Brexafemme	Scynexis	Vulvovaginal candidiasis	1,3-Beta-glucan synthase inhibitor	USA	September	N	N	Y
idecabtagene vicleucel	Abecma	Bristol-Myers Squibb	Multiple myeloma	T cell stimulant	USA	May	N	Y	Y
imeglimin	Twymeeg	Sumitomo Dainppon Pharma/ Poxel	Type 2 diabetes	Gluconeogenesis inhibitor	Japan	September	N	N	N
imlifidase	Idefirix	Hansa Biopharma	Kidney transplant rejection	Endopeptidase stimulant	Finland, the Netherlands, Sweden	September	Y	N	Y
inclisiran	Leqvio	Novartis	Heterozygous familial hypercholesterolaemia	PCSK9 inhibitor	The EU	November	N	Y	N
infigratinib	Truseltiq	BridgeBio Pharma	Biliary cancer	FGF receptor 1/2/3 tyrosine kinase inhibitor	USA	June	N	Y	Y
inolimomab	Leukotac	Mediolanum Farmaceutici	Graft-versus-host disease	Interleukin 2 receptor antagonist	France	January	N	Y	Y
lazertinib	Leclaza	Genosoco/ YuHan	Non-small cell lung cancer	EGFR kinase inhibitor	South Korea	Auguat	N	N	N
lisocabtagene maraleucel	Breyanzi	Bristol-Myers Squibb	Diffuse large B-cell lymphoma/ follicular lymphoma	T cell stimulant	USA	May	N	Y	Y
lonafarnib	Zokinvy	Eiger BioPharmaceuticals	Progeria	Farnesyltransferase inhibitor/P glycoprotein inhibitor^/MRP inhibitor^	USA	January	Y	Y	Y
loncastuximab tesirine	Zynlonta	Auven Therapeutics	Diffuse large B-cell lymphoma	DNA inhibitor	USA	May	N	Y	Y
maralixibat	Livmarli	Mirum Pharmaceuticals/ Lumena	Alagille syndrome	Ileal bile acid transporter inhibitor/Sodium/bile acid co-transporter inhibitor	USA	November	N	Y	N
margetuximab	Margenza	MacroGenics	Breast cancer	ErbB-2 antagonist	USA	March	N	N	N
maribavir	Livtencity	Takeda/GlaxoSmithKline	Cytomegalovirus infection	Cytomegalovirus UL97 protein kinase inhibitor	USA	December	Y	Y	Y
mobocertinib	Exkivity	Takeda	Non-small cell lung cancer	Tyrosine kinase inhibitor/ ErbB-2 antagonist/EGFR antagonist	USA	September	N	N	Y
molidustat	Musredo	Bayer	Renal disease-induced anaemia	HIF prolyl hydroxylase inhibitor	Japan	April	N	N	N
molnupiravir	Lagevrio	Merck & Co/ Ridgeback Therapeutics	COVID-19 infection	Viral replication inhibitor	USA	December	N	N	N
naxitamab	Danyelza	Y-mAbs Therapeutics	Neuroblastoma	Ganglioside antigen GD2 antagonist	USA	March	N	Y	Y
nirmatrelvir	Paxlovid	Pfizer	COVID-19 infection	SARS 3 cysteine-like protease inhibitor	USA	December	Y	N	N
odevixibat	Bylvay	Albireo Pharma	Progressive familial intrahepatic cholestasis	Ileal bile acid transport inhibitor	USA	August	N	Y	Y
olanzapine + samidorphan**	Lybalvi	Alkermes	Bipolar disorder/ Schizophrenia	Opioid delta/kappa/mu receptor agonist/ Opioid delta/kappa receptor antagonist/ 5 Hydroxytryptamine 2A/2C/6 receptor antagonist/Dopamine D1/D2/D3/ D4 receptor antagonist	USA	October	N	N	N
oliceridine	Olinvyk	Trevena	Post-operative pain	Opioid mu receptor agonist	USA	January	N	N	N

TABLE 1:
New active substance launches, 2021 *(Cont'd)*

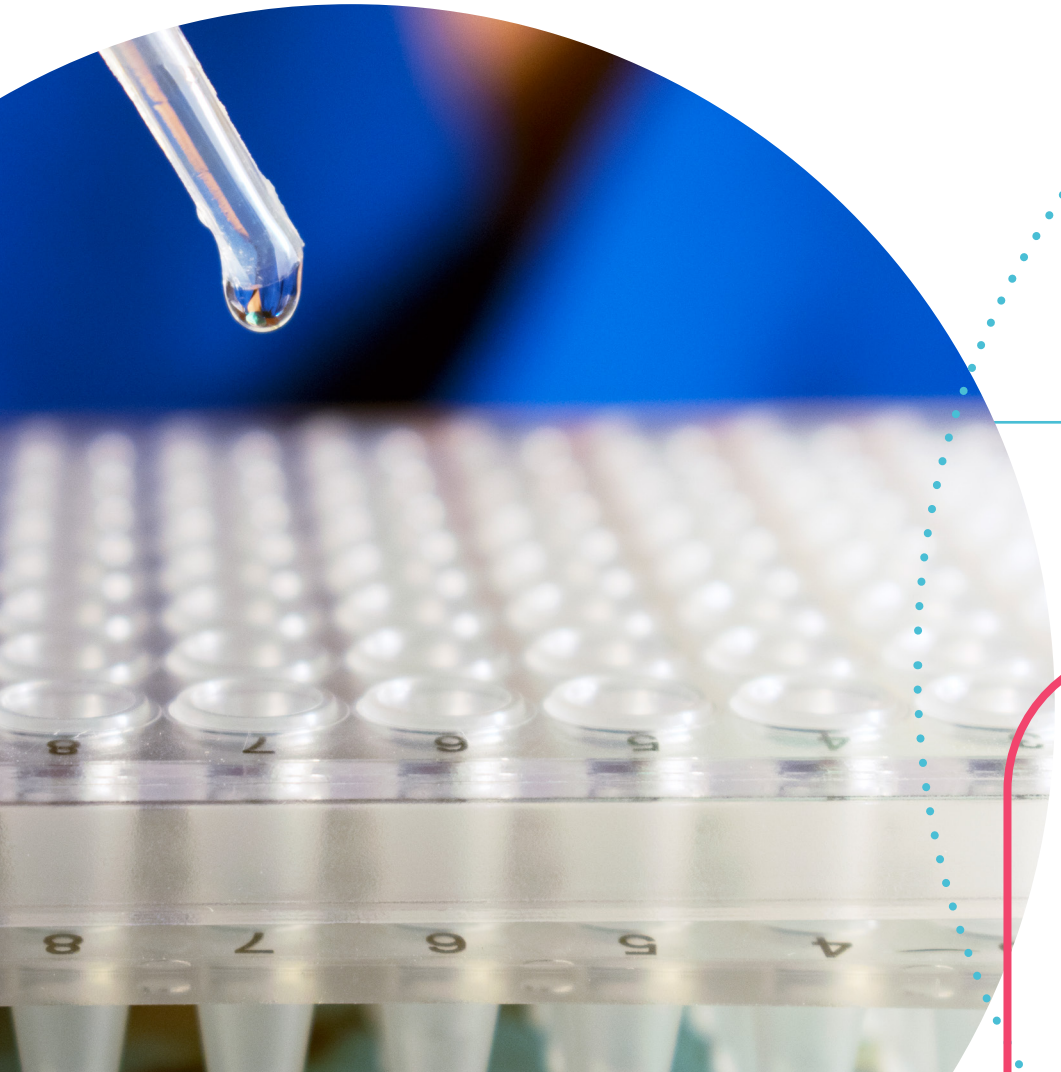
GENERIC DRUG NAME	TRADE NAME	COMPANY	DRUG DISEASE	MECHANISM OF ACTION	DRUG COUNTRY	MONTH OF LAUNCH	FIRST-IN-CLASS?	RARE DISEASE?	ORPHAN DRUG STATUS?
olverembatinib	Nerike	Ascentage Pharma/Guangzhou Pharmaceuticals/Innovent Biologics	Chronic myelogenous leukemia	Bcr-Abl inhibitor/C-kit inhibitor	China	December	N	Y	N
orelabrutinib	Yinuokai	Ascentage Pharma/Guangzhou Pharmaceuticals/Innovent Biologics	Chronic lymphocytic leukaemia/Mantle cell lymphoma	Bruton tyrosine kinase inhibitor	China	January	N	Y	N
pabinafusp alfa	Izcargo	JCR Pharmaceuticals	Mucopolysaccharidosis II	Iduronate 2 sulfatase stimulant	Japan	May	N	Y	Y
pamiparib	Partruvix	BeiGene	Ovaran cancer	Poly ADP ribose polymerase 1/2 inhibitor	China	May	N	Y	N
pegcetacoplan	Empaveli	Apellis	Paroxysmal nocturnal haemoglobinuria	Complement C3 convertase inhibitor	USA	July	Y	Y	Y
penpulimab	Annikol	Akeso Biopharma	Hodgkin's lymphoma	PD-1 antagonist	China	August	N	Y	N
pneumococcal vaccine, 20-valent, Pfizer	Prevnar20	Pfizer	Pneumococcal infection prophylaxis	Immunostimulant	USA	July	N	N	N
ponesimod	Ponvory	Johnson & Johnson	Relapsing-remitting multiple sclerosis	Sphingosine 1-phosphate 1 receptor agonist	EU/USA	July	N	N	N
regdanvimab	Regkirona	Celltrion	COVID-19 prophylaxis and treatment	Surface glycoprotein (SARS-CoV-2) antagonist	South Korea	November	N	N	N
relmacabtagene autoleucel	Relma-cel	JW Therapeutics	Diffuse large B-cell lymphoma	T cell stimulant	China	November	N	Y	N
savolitinib	Orpathys	Hutchmed/AstraZeneca	Non-small cell lung cancer	MET tyrosine kinase inhibitor	China	July	N	N	N
setmelanotide	Imcivree	Rhythm Pharmaceuticals	POMC deficiency/Leptin receptor deficiency obesity	Melanocortin MC-4 receptor agonist/Melanocyte stimulating hormone receptor agonist	USA	September	N	Y	Y
somapacitan	Sogroya	Novo Nordisk	Growth hormone deficiency	Growth hormone receptor agonist	USA	October	N	N	N
sotagliflozin	Zynquista	Lexicon Pharmaceuticals	Type 1 diabetes	Sodium/glucose cotransporter 2/1^ inhibitor	EU/USA	December	Y	N	N
sotorasib	Lumakras	Amgen	Non-small cell lung cancer	K-Ras inhibitor	USA	August	Y	N	Y
sotrovimab	Xevudy	GlaxoSmith-Kline	COVID-19 infection	Surface glycoprotein (SARS-CoV-2) antagonist	Australia	October	N	N	N
surufatinib	Sulanda	Hutchmed	Neuroendocrine cancer	VEGFR-1/2/3 tyrosine kinase inhibitor/FGF receptor 1 tyrosine kinase inhibitor/Colony stimulating factor 1 receptor antagonist	China	January	N	N	Y
telitacicept	TaiAi	RemeGen/Rongchang Pharmaceuticals	Systemic lupus erythrematosus	B-cell activating factor inhibitor/APRIL inhibitor^	China	August	Y	N	N
teserpaturev	Delytact	Daiichi Sankyo	Brain cancer/Glioma	Immuno-oncology therapy	Japan	November	N	Y	Y
tirbanibulin	Klisyr	Almirall	Actinic keratosis	Src inhibitor/Tubulin polymerization inhibitor	USA	February	N	N	N
tisotumab vedotin	Tivdak	Genmab/Seagen	Cervical cancer	Tubulin inhibitor	USA	September	N	N	N
tralokinumab	Adbry	Leo Pharma	Atopic eczema	Interleukin 13 antagonist	USA	December	Y	N	N
trilaciclib	Cosela	Boehringer Ingelheim/G1 Therapeutics	Non-small cell lung cancer	Cyclin-dependent kinase 4/6 inhibitor	USA	March	N	Y	N

TABLE 1:
New active substance launches, 2021 *(Cont'd)*

GENERIC DRUG NAME	TRADE NAME	COMPANY	DRUG DISEASE	MECHANISM OF ACTION	DRUG COUNTRY	MONTH OF LAUNCH	FIRST-IN-CLASS?	RARE DISEASE?	ORPHAN DRUG STATUS?
umbralisib	Ukoniq	Rhizen Pharmaceuticals/TG Therapeutics	B-cell/follicular lymphoma	PI3 kinase delta inhibitor/ Casein kinase 1 inhibitor^	USA	August	Y	Y	Y
upacicalcet sodium hydrate	Upasita	EA Pharma/ Eisai/Sanwa Kagaku Kenkyusho	Secondary hyperparathyroidism	Calcium-sensing receptor agonist	Japan	September	N	Y	N
varicella zoster vaccine, Green Cross	Suduvax-II	GC Pharma	Varicella zoster infection prophylaxis	Immunostimulant	South Korea	September	N	N	N
vericiguat	Verquvo	Bayer/Merck & Co	Chronic heart failure	Guanylate cyclase stimulant	Japan	September	N	N	N
voclosporin	Lupkynis	Aurina Pharmaceuticals	Lupus nephritis	Calcineurin inhibitor	USA	January	N	Y	N
vosoritide	Voxzogo	BioMarin	Achondroplasia	Natriuretic peptide agonist	France/ Germany	September	N	Y	Y
zimberelimab	YuTuo	Harbin Gloria Pharmaceuticals	Hodgkin's lymphoma	PD-1 antagonist	China	September	N	Y	N

Source: Pharmaprojects®, February 2022

* Both components are NASs
** Just this component is a NAS
^ Novel mechanism of action



There's a lot to digest in that jumbo-sized list of new drugs, so let's start to break those new drugs down by a number of different parameters. Table 2 lists all of the companies which launched more than one NAS during the year, and where they fell in our chart of companies by pipeline size, on the basis that the best performance could be considered the most drugs delivered from the smallest pipeline. It also includes for reference the performance of any top 10 pharmas which didn't manage to bring to the market two or more drugs.

Spearheading the charge into new territory last year was UK-headquartered AstraZeneca, the only company to successfully introduce five new active substances. As well as its renowned COVID-19 vaccine, and its combination anti-COVID antibody product Evusheld (both of which, more later), it delivered a novel NAS for lupus in the shape of Saphnelo (anifrolumab) and, in China, launched a new MET tyrosine kinase inhibitor for use against non-small cell lung cancer, Orpathys (savolitinib). This was more than double what it delivered in 2020, when Gilead and Pfizer tied for pole position with four NASs apiece. Pfizer was back on the leaderboard with two 2021 NASs, but it looks like Gilead ran out of gas.

Four companies launched a trio of salvos into NAS land, with Bayer having the best NAS launch to pipeline size ratio, being only fourteenth in terms of size of its overall R&D portfolio. It was joined here by Johnson & Johnson, Merck & Co, and GlaxoSmithKline, the latter of which also launched three drugs in 2020, and thus could be said to be the most consistent performer during the pandemic years. There follows a dozen companies with

TABLE 2:
Top company NAS launch performance, 2021

COMPANY	NO. OF NAS LAUNCHES 2021	POSITION BY PIPELINE SIZE
AstraZeneca	5	6
Bayer	3	14
GlaxoSmithKline	3	11
Johnson & Johnson	3	8
Merck & Co	3	7
Guangzhou Pharmaceuticals	2	4,149
RemeGen/Rongchang Pharmaceuticals	2	457
Ascentage	2	336
BridgeBio Pharma	2	100
Hutchmed	2	212
Innovent Biologics	2	54
Sumitomo Dainippon	2	25
Eisai	2	18
Jiangsu Hengrui Pharmaceuticals	2	16
Pfizer	2	5
Bristol Myers Squibb	2	4
Takeda	2	3
Novartis	2	1
Eli Lilly	1	10
Sanofi	1	9
Roche	0	2

Source: Pharmaprojects®, February 2022

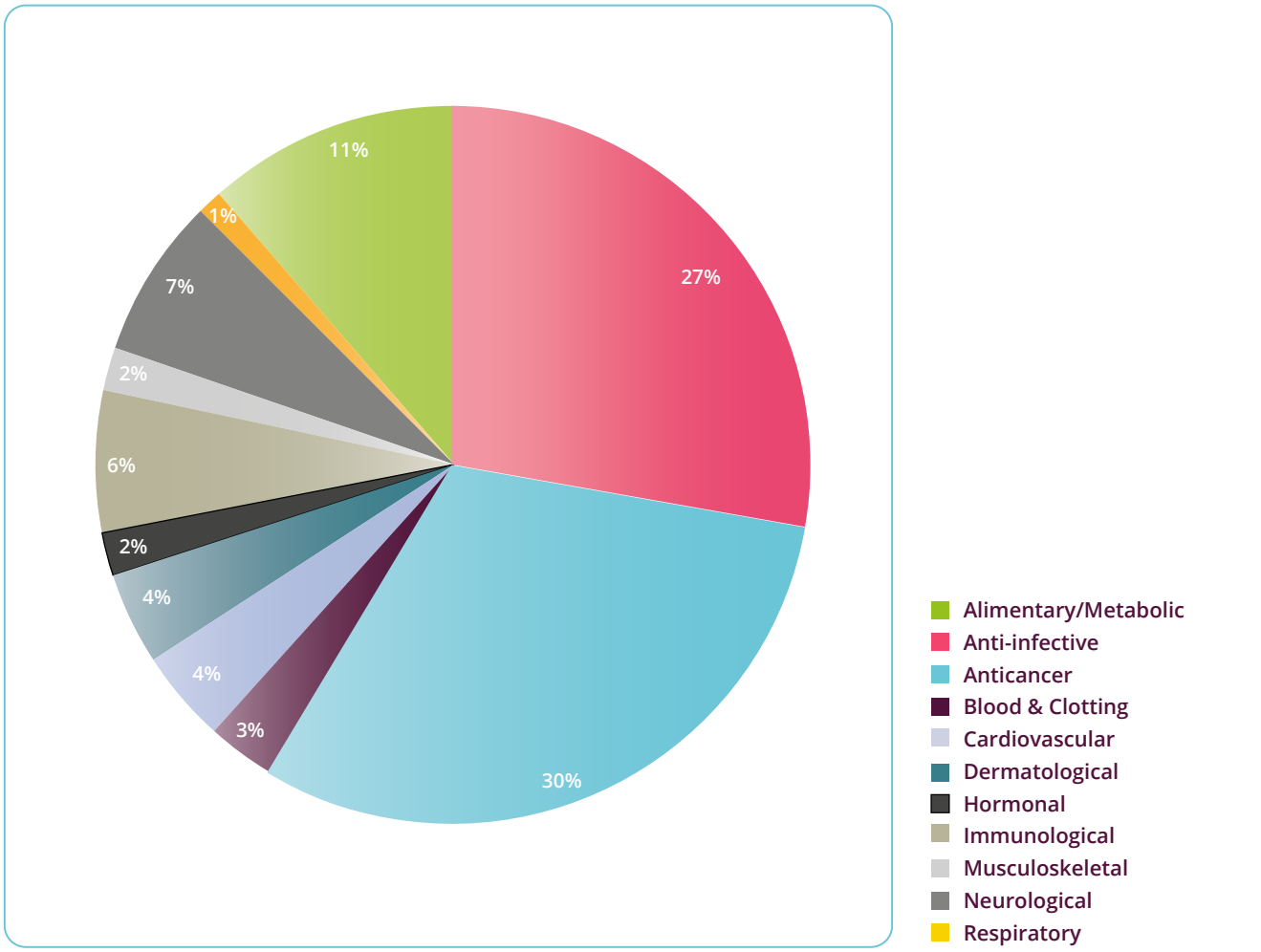
a pair of agents in the arrivals lounge. These include five companies outside of the top 25 by pipeline size, four of which are Chinese, with Guangzhou Pharmaceuticals being the company with the biggest NAS launch to pipeline size ratio. They are joined by BridgeBio Pharma in the US, which launched two drugs for rare diseases there: Nulibry (fosdenopterin) and Truseltiq (infigratinib) for molybdenum cofactor deficiency and biliary cancer, respectively. A further seven of the dual drug deliverers are top 25 companies, including one of the first Chinese-headquartered firms to enter the upper echelons of our chart, Jiangsu Hengrui Pharmaceuticals.

Like last year, only three top 10 pharmas missed out on providing more than one new drug, with Roche finding itself unable to get anything over the line during calendar 2021. But it did launch three new drugs in 2020. Overall, the biggest 10 pharma companies, which are now just developing 4.6% of all drugs, were involved in launching 18 of the 97 NASs, or 18.6%, suggesting that the might of Big Pharma still has the muscle to get its drugs all the way to the finish line. But this is only part of the story. Revisit Table 1 and look at how many companies last year delivered NASs without any involvement from a sizeable partner. There are plenty of names there which you might not even have heard of, never mind them not being household names. In many ways, 2021 was a year when the pharma minnows came good.

Moving on to carve up the NAS continent into its various different therapeutic area habitats, cancer has reasserted itself at the summit, with the largest number of novel introductions: 30. This is quite an uptick from the 22 launched during 2020, and, given the pre-eminent state of cancer drugs in the overall pipeline, sees order being restored after it was temporarily overthrown last time. But the COVID bounce for anti-infectives is clearly far from over. It comes in second with 27 NASs, but even though it was forced into second place, it is still an enhanced total, comparable to the 28 it launched in 2020, and way beyond recent historic levels (2019's number was just 5). Between them, these two therapeutic areas accounted for 59% of all new active substances, even more than the 58% reported twelve months prior.

Elsewhere, the alimentary/metabolic group hit double-digits, easily surpassing the three delivered in 2020, to become 2021's third most successful therapeutic area. It pushed neurologicals down to fourth with 7, followed by immunological agents with 6. There were slim pickings for the remainder of the therapeutic groups.

FIGURE 2:
2021 NAS launches by therapeutic group



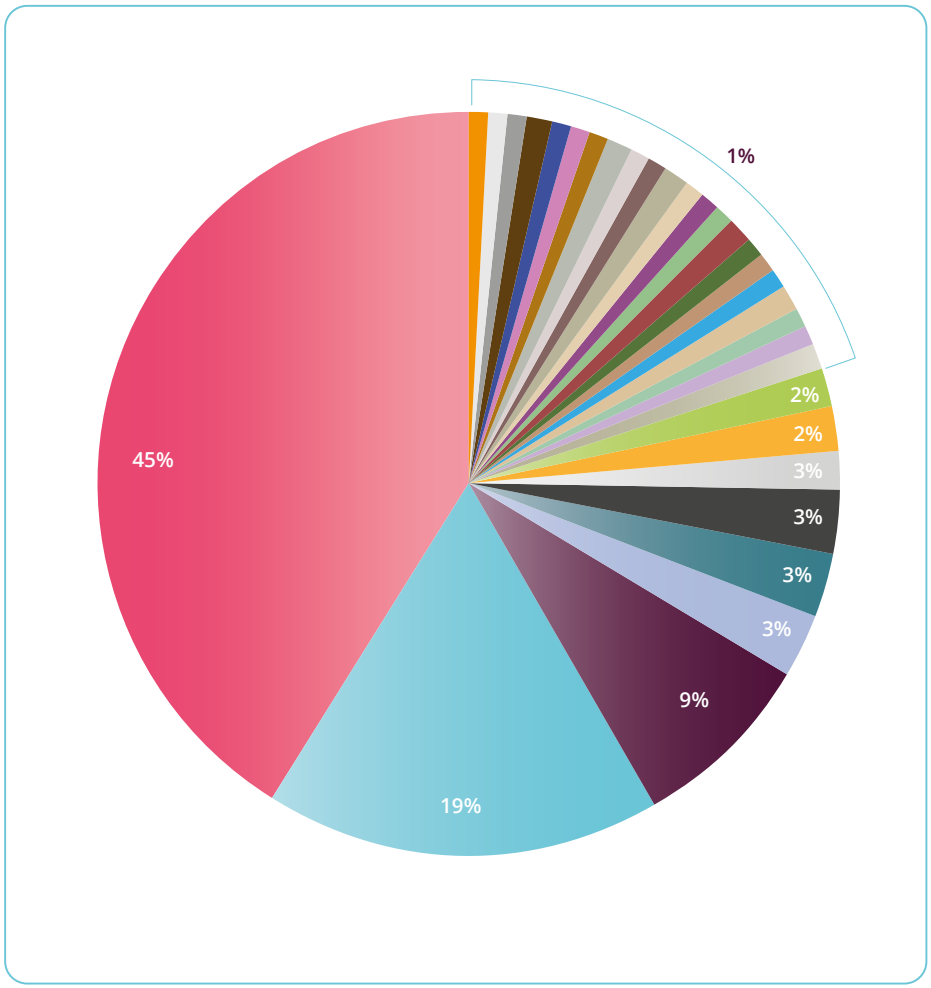
Source: Pharmaprojects®, February 2022

2021 was a particularly successful year for biotechnology-based drugs, with 44 (45%) of the NASs falling into this class. This far surpassed the 33% seen last year, and is also just a little higher than the proportion of drugs in the overall pipeline of this type. Nineteen of these were monoclonal antibodies (spread across 17 products, as two are dual MAb combos), plus an additional two bispecific antibodies. There were eight recombinant vaccines, four gene therapies, four antibody-drug conjugates, three chimeric antigen receptor T-cell (CAR-T) therapeutics, and three fusion proteins. It was a relatively quiet year for RNA-based therapeutics, with just a single antisense therapy (BioMarin and Sarepta Therapeutics' muscular dystrophy drug Amondys 45 [casimersen]) and a sole RNA interference agent (Alnylam and Novartis's Leqvio [inclisiran]).

In a survey from 2016 on the leading reasons why people chose a particular location for their vacation, the top answer was 'to experience the culture'. Next came financial considerations ('the accommodation had a good price'; 'the flight had a good price'). Bottom of the list was 'it was off the beaten track'. For pharma, the choice of first country to launch a NAS is seemingly a mixture of cultural and financial grounds: where the company is based and the size of the market. Nonetheless, as Figure 3 shows, some drugs still made their debuts in some of the more off-the-grid markets [note that some drugs have more than one country/market as their first].

Not surprisingly, the US retains its stranglehold on this metric, with 46% of the NAS launches occurring there first. However, this is an erosion of its 2020 figure of 54%. But really, the developing story of new active substance launches belongs to China. In 2020, it was the debut market for just seven of the 82 drugs; last year, this was up to 19, or around one fifth. With the exception of AstraZeneca's Orpathys, all of these were locally originated drugs, developed by Chinese companies. Like elsewhere, cancer has become China's main focus, with 12 of the Chinese NASs having an oncological focus. China zoomed past Japan in terms of being the pre-eminent Asian country for first launches,

FIGURE 3:
2021 NAS launches by country/region



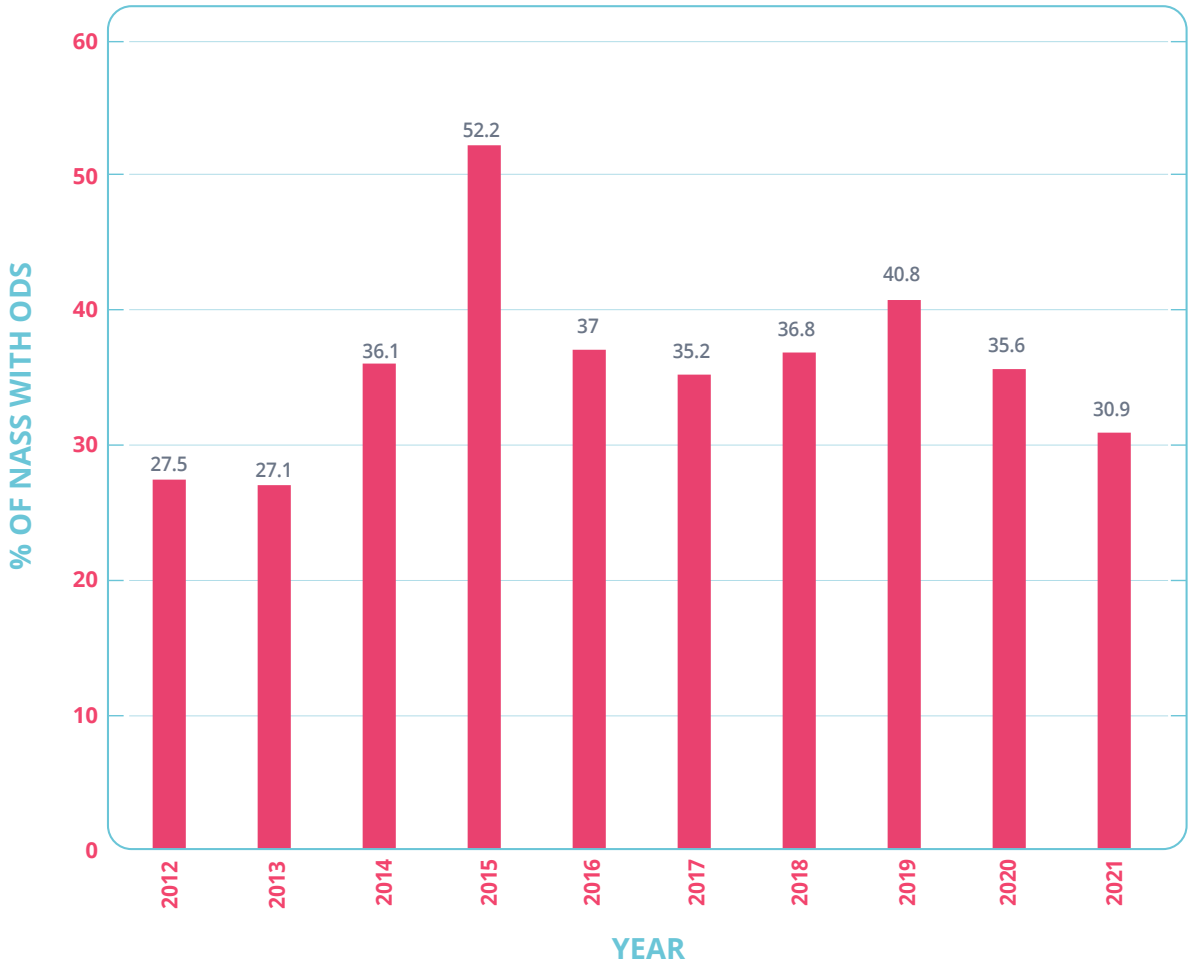
Source: Pharmaprojects®, February 2022

with the latter booking just nine last year. Europe is languishing well behind China now, with just 11 of the NASs being first rolled-out there.

The righthand-most columns of Table 1 give an indication of whether our NASs were launched for rare diseases, and whether these developments were encouraged by concomitant orphan drug designations. A rare disease is defined as one with a prevalence lower than one in every 2,000 people in the EU, or affecting fewer than 200,000 people in the US (equivalent to around one in every 1,600 people). Last year, 39 of the 97 NASs were developed for rare diseases, which represented both an increase in the overall number from 2020, which reported 28, and a rise in the percentage (40.2% vs 34.1%). However, the percentage which had orphan drug status granted for the disease they got approved for fell back, to just 30.9%. Why is that? It could simply be a function of the increased number of NASs which debuted in countries which don't have an orphan drug status scheme, such as China. As Table 1 showed, generally, in the West, rare diseases and ODS still go mostly hand-in-hand.

So, our guidebook of the demographics and culture draws to a close, and it's time to delve into the unique 'must-see' places of interest in our 2021 NAS country tour.

FIGURE 4:
Percentage of NAS launches with an orphan drug designation, 2012–21



Source: Pharmaprojects®, February 2022
NOTE: 2016–21 figures refer only to drugs with orphan drug status for their marketed indication in their marketed country.

The Novel NASs of 2021:

New vistas open up in cancer and inflammation, as pharma plants its flag across multiple new territories

Travel, like pharma R&D, begins with discovering something new. Even in our interconnected 21st century world, there are still parts of our planet which are, to all extents and purposes, unexplored and unknown to most of the human race. These range from mountains in Bhutan which have never been climbed, down to what paradoxically is the biggest mountain range on the planet, the mid-ocean ridge, the extent of which has only recently been fully mapped, due to the fact that it is entirely at the bottom of the ocean. Then there is the southern Namib desert in Namibia, thought to be largely unexplored, mainly because of the fact that there isn't really much there to explore anyway. At the other end of the scale, there are areas of dense jungle in the Amazon rainforest which remain unmapped and still throw up unknown tribes of indigenous people, seemingly completely cut off from the outside world. Then there are numerous tiny islands sprinkled around the globe about which little is known, such as the enigmatic North Sentinel Island – a tiny dot on the map, ostensibly owned by India, but actually protected by a three-mile exclusion zone as the native islanders remain hostile to outsiders.

Despite these pockets of wonder yet to be delved into, our world is now pretty well charted, with the Google Earth project taking things to the next level this century. In comparison, our understanding of diseases and the development of drugs to treat them is probably only in the Middle Ages, with the completion of the Human Genome Project and the associated biotech revolution probably being akin to the discovery of the 'New World'. In other words, we've made some great leaps forward, but there are still entire continents of pathology of which we only have the scantest maps as yet. There is much to explore, much to learn, much to discover.

The good news is that, every year, the pharmaceutical industry brings to market a set of drugs which open up brand new vistas of never-before-seen ways to treat diseases, by bringing not just new drugs, but new kinds of drugs, to the market – the novel NASs. Our strict definition of novelty here is that a drug is novel if it's the first to reach the market with a particular mechanism of action, and that's what we'll focus on here in this section of the report. Of course, there are other forms of innovation, and other reasons why drugs might be considered significant, and we'll come to those later.

During 2021, using this definition, 17 were first-in-class. That's actually exactly the same number we saw in 2020, but given the overall NAS total is higher, it means that the percentage of 2021 NASs classed as novel has fallen: from 21.5% down to 17.5%. It would though be churlish to suggest that 2021 – the year which saw the pharma industry become the conquistadors of COVID – was not a big year for innovation. It's been an anomalous period of time in so many ways, with the virus diverting the gaze of many. Let's instead here celebrate the new territories which pharma conquered, despite everything thrown in its path.

We've already seen how cancer is leading the way in the total number of R&D drugs, share of pipeline, and, in this report, new active substances launches. And it's also near the front of the queue for speedy boarding onto the plane in terms of delivering novelty, with three NASs classed as novel by our definition. This is a slight improvement on 2020, which, despite the enormous oncology pipeline, only saw two innovative anticancers cross the finish line. Even so, it might to some feel like arriving at a hotel which doesn't live up to the brochure pictures.

We saw in the main Pharma R&D Report that one of the drug mechanisms of action which experienced the biggest increase in popularity was K-Ras inhibition, and 2021 saw the first drug of this type reach the market. This was

Amgen's Lumakras (sotorasib), which gained the green light for non-small cell lung cancer in the US initially, followed by a slew of subsequent approvals elsewhere. As such, it beat no fewer than 77 drugs in active development to the finish line, in the most crowded field for any of last year's new mechanisms. Closest behind in the rear-view mirror is Mirati Therapeutics' adagrasib, which is currently awaiting approval, also for NSCLC in the US. Meanwhile, Amgen is looking to expand its agent into a number of other tumour types, with colorectal being the most advanced, in Phase III.

Merck & Co was also on the tour bus with its Welireg (belzutifan), the world's first hypoxia-inducible factor 2 alpha antagonist. HIF-2α is involved in von Hippel-Lindau disease, a syndrome characterised by visceral cysts and benign tumours which often undergo subsequent malignant transformation. The full indication for which this new drug has been approved is for use in patients with von Hippel-Lindau disease who require therapy for associated renal cell carcinoma, central nervous system haemangioblastomas, or pancreatic neuroendocrine tumours. Unsurprisingly, the drug received orphan drug status in the US for this niche condition, and has received the same leg-up in Australia. The drug came into Merck's orbit following its 2019 acquisition of Peloton Therapeutics.

The final anticancer novel NAS for 2021 was developed away from Big Pharma, under a collaboration between Rhizen Pharmaceuticals and TG Therapeutics. Their Ukoniq (umbralisib) is a PI3 kinase delta inhibitor with the additional, novel pharmacology of casein kinase 1 inhibition. Completing a clean sweep for novel oncological introductions in the US, this drug is available for use in adult patients with relapsed or refractory marginal zone lymphoma after at least one prior anti-CD20 based regimen and adult patients with relapsed or refractory follicular lymphoma after at least three prior lines of systemic therapy. The review process here was expedited by both priority review and breakthrough designation in the US, and follow-on indications include chronic lymphocytic lymphoma (for which it has been filed) and diffuse large B-cell lymphoma.

It was an unusually good year for the autoimmune and inflammation area, which under its broadest definition actually delivered the most innovation, with six drugs with previously undeveloped mechanisms reaching their destinations. Two of these were for systemic lupus erythematosus. AstraZeneca's Saphnelo became the first interferon (type I) receptor antagonist when it was launched in Japan in November. Earlier in the year, and completing the pair of the only two drugs to launch first in countries outside the US and EU, was the first APRIL inhibitor, Tai'ai (telitacicept). This is notable as it's a still (as yet) rare example of a completely novel mechanism to come out of China. It was developed there by RemeGen, part of Rongchang Pharmaceuticals, and is a fusion protein which jointly targets BLyS and the aforementioned novel target APRIL. APRIL, or CD256, is a proliferation-inducing ligand which is important in B-cell development. It's another landmark on China's long march from being just a generics-developing country, via me-too drugs, to producing new agents of genuine novelty.

The complement system is a complex cascade involved in clotting as well as inflammatory processes, and is the target for two more of our 2021 novel NASs, one of which falls in the latter bucket. Tavneos/Vynpenta (avacopan) has been developed by ChemoCentryx for use in severe active anti-neutrophil cytoplasmic autoantibody-associated vasculitis, specifically granulomatosis with polyangiitis and microscopic polyangiitis – syndromes whereby blood vessels are destroyed by inflammation. The drug, a small molecule, is the first to target complement C5a receptor 1. Potential follow-on indications include haemolytic uraemic syndrome, G3 glomerulopathy, and hidradenitis suppurativa.

Kidney transplant rejection is the focus of our only enzyme-based novel NAS of the year. Hansa Biopharma's Idefirix (imlifidase) has been launched in the US; it's the first drug classified as an endopeptidase stimulant, and is actually a proteolytic enzyme derived from the bacterium Streptococcus pyogenes. It has a high affinity for IgG antibodies, hence its use in the treatment of organ transplant rejection. It also has potential use in Guillain-Barré syndrome.

In the dermatological inflammation arena, we have two new novel agents, both based around interleukin antagonism. Adbry (tralokinumab) is a new monoclonal from Leo Pharma for the treatment of atopic eczema, which just squeaked its launch in at the end of the year. It is the first interleukin-13 antagonist to successfully complete its voyage to the market, docking ahead of similar monoclonals from AbbVie/Bristol Myers Squibb and Almirall/Eli Lilly in the shapes of cendakimab and lebrikizumab, respectively, both of which are still far out to sea in Phase III trials. We also saw the introduction of UCB's Bimzelx (bimekizumab), which is a dual interleukin-17A and -17F antagonist, and it's the latter of these two pharmacologies which hasn't been seen in a launched drug before. This agent debuted in Germany in September for use in moderate-to-severe plaque psoriasis, and other launches in Sweden, the UK and then the Netherlands swiftly followed. Judging by the number of times the drug is mentioned in UCB's annual report, the company clearly feels that, with prevailing winds, this product could become head of its fleet.

The travel industry has undoubtedly suffered heavily during the past two pandemic years. Overseas trips were, from many countries, completely forbidden at many points. Almost as bad, in the UK at least, we faced periods where the rules would change at very short notice. I myself experienced this when trying to go on holiday in September 2020. With international travel from Great Britain having restarted, and having booked a vacation to Ibiza in Spain, two weeks before departure, Spain went on the UK's 'red list', making a holiday there untenable. I quickly cancelled everything and rebooked a trip to Croatia – only to find that country fall to the red list a week later, at which point, I gave up and decided to holiday in Yorkshire instead!

This on-again, off-again uncertainty would sound familiar to the developers of the year's most controversial drug launch, Aduhelm (aducanumab). This novel NAS is the first beta-amyloid protein antagonist to reach the market, but neither its journey to get there, nor its fate after its arrival, have exactly followed straightforward trajectories. Many drugs attempting to use the beta-amyloid hypothesis to voyage to find the Golden Fleece of a treatment for Alzheimer's disease found themselves shipwrecked and all at sea at Phase III development. Notable casualties finding their hopes dashed on the rocks in recent years included Pfizer and Johnson & Johnson's bapineuzumab, and Eli Lilly's solanezumab. Aduhelm's developers, Biogen and Eisai, have found themselves manning the lifeboats too previously: this drug began Phase III trials as far back as 2015, and the first two trials ran aground in 2019 after a negative futility analysis. But after a spell on a desert island, the companies built a raft for the monoclonal antibody and refloated its Phase III effort, crunching the data differently to show a much-debated efficacy signal in one of the trials. Emboldened, the companies filed an NDA, but the FDA's Advisory Committee wasn't impressed and decided that the cognitive benefit wasn't yet proven, voting 10 to 1 against approval. It was to many observers' surprise, then, when the FDA gave the drug the thumbs up in June, on the basis of the positive biomarker data alone.

But it has been far from plain sailing since. Three Advisory Committee members resigned over the decision, amid a general outcry from many in the industry and beyond. Nonetheless, Biogen launched the drug in the US in July, promising to complete a confirmatory trial.

However, payers in the US, such as Medicare, have decided that they won't pay for the drug, leaving it in the twilight zone of being approved but largely unavailable, as few are convinced that it actually works. Thus, sales have barely made it out of port. Despite many continuing to doubt the entire validity of the amyloid hypothesis in Alzheimer's, one side effect of this salty saga has been that it has given the kiss of life to several previously beached beta-amyloid protein antagonists, notably the aforementioned solanezumab.

On a different shore, anti-infectives last year yielded just two novel NASs, one of which, unsurprisingly came along with COVID: Pfizer's much-lauded Paxlovid (nirmatrelvir, administered with ritonavir to extend its half-life). This may have been the second direct anti-SARS-CoV-2 antiviral to make it to market, but clinical trial results demonstrated it to be more effective than Merck & Co/Ridgeback's Lagevrio (molnupiravir), it being found to reduce the risk of hospitalisation or death by 89%, compared to 50% for the latter. It also qualifies as novel, being the first SARS 3 cysteine-like protease inhibitor to be launched, with the field for Pfizer looking pretty clear (only Shionogi's Phase III candidate S-217622 is currently beyond the preclinical phase). The Merck drug's mechanism is less clear cut: it's reported to cause mutations in RNA synthesis by acting as a dummy amino acid, so we have it classified as a general viral replication inhibitor for now, thus rendering it non-novel.

Despite the COVID hegemony, other viruses are available. Takeda and GlaxoSmithKline teamed up to deliver Livtencity (maribavir), the world's first cytomegalovirus UL97 protein kinase inhibitor, to tackle cytomegalovirus infection. CMV is already endemic, but can be problematic in those with immunosuppressive disorders. It was a serious problem during the height of the AIDS crisis, when it caused a lot of patients to lose their sight via CMV retinitis. Although this threat has largely passed, it's good to have an additional selection available in the therapeutic minibar. The fact that serious CMV infections are relatively rare now is also a reminder of how viral threats can ebb and flow with some rapidity.

Talking of rare, if you want something really niche, you might want to embark on a trip to see the sights of BridgeBio Pharma's second product to market, as we move to look at novel new active substances for metabolic diseases. Nulibry is a molybdenum cofactor replacement therapy for molybdenum cofactor deficiency. This is an ultrarare genetic disorder caused by a mutation in the MOCS1 gene, which usually leads to death within months of birth. As is often the case with drugs developed for diseases which only affect a very small number of patients, the life-saving treatment comes with an eye-watering price tag – $500,000 per year in this case. With only around 150 patients to treat worldwide however, such a high cost was to be expected if Bridge is to recoup its development costs.

Another somewhat obscure backwater is progeria. Also known as Hutchinson-Gilford syndrome, progeria, as the name suggests, is a condition whereby patients appear to undergo accelerated aging, leading to death in the second decade of life. It's extremely rare, being thought to affect one in 18 million people. Riding to the rescue here is Eiger BioPharmaceuticals, which licensed in Zokinvy (lonafarnib) from Merck & Co. The drug has multiple actions, two of which are novel in a launched drug: P-glycoprotein inhibition and MRP inhibition. Interestingly, this agent also has activity against an infectious pathogen, the hepatitis D virus. Zokinvy's price makes Nulibry look like a bargain basement cheap awayday; coming in at surplus to $1m per year, it's now the most expensive drug on the books in the US.

Somewhat more prosaic is our third novel NAS under the metabolic sunshade, Lexicon Pharmaceuticals' Zynquista (sotagliflozin), which

is for the far more prevalent condition of type 1 diabetes. While over 20 inhibitors of sodium/glucose cotransporter 2 are already on the market, this is the first drug which combines this mechanism additionally with sodium/glucose cotransporter 1 inhibition. It is also awaiting approval for use in type 2 diabetes and heart failure.

Bridging the lands of metabolic and haematological drug development, Apellis has developed Empaveli (pegcetacoplan), which returns us to the complement cascade theme park mentioned earlier. It's the first complement C3 convertase inhibitor, and was launched in the US last year for paroxysmal nocturnal haemoglobinuria, another rare disease, but this time one which is acquired rather than inherited. Here, the complement system destroys red blood cells, producing a haemolytic anaemia. Apellis's agent is a pegylated synthetic peptide, which is also being developed for the ophthalmological condition of geographic atrophy.

Lastly, we have an innovation in the big tent of cardiovascular therapeutics. Regeneron launched Evkeeza (evinacumab) for the rare lipid disorder homozygous familial hypercholesterolaemia. While there has been considerable activity in this disease in recent years with the launch of the PCSK9 inhibitors, this drug takes a different tack, and is the debut of the strategy of angiopoietin-like 3 inhibition onto the market. The target protein inhibits the hydrolysis of HDL phospholipid and thus increases the proportion of the so-called 'good' cholesterol. This is another case of a drug being successfully developed against a condition which is not just rare, but is characterised as ultrarare, with just 1,300 patients suffering from it in the US. It means that six of the 17 novel NASs of the year were developed for use in rare diseases. In drug R&D, as in travel, a journey off the beaten track can be the most rewarding.

Other Notable NASs

Conquering COVID's highest peaks

In the second of what were two extraordinary years, we have to start our review of other notable NASs which may not be classed as novel by our definition, but are nonetheless significant, with another look at COVID country. No other single disease can ever have dominated drug introductions so much in a single year, with 17 new drugs and vaccines in total (18 individual NASs, as one product is a combination therapy). While no fewer than five vaccines (those from Pfizer/BioNTech, Moderna, Beijing Institute of Biological Products, Sinovac, and Russia's Gamaleya Institute) made the list for 2020, and thus were launched within a year of the pandemic's emergence, 2021 should really be styled as the year of the COVID vaccine. It was last year that the global vaccination roll-out really happened, with most of us having received three doses of the jabs during that calendar year. And COVID vaccines can't be missed in our list of NAS launches, there being 11 of them. 2021 began with the launch of the Oxford University and AstraZeneca version, but this vaccine had a bit of a bumpy ride subsequently, perhaps unfairly. Despite the fact that AZ, unlike Pfizer and Moderna, was offering its vaccine as a non-profit option, the discovery of a very rare side-effect of blood clots tarnished its reputation somewhat, and it subsequently became embroiled in post-Brexit political machinations. Elsewhere, aside from the Janssen jab, most of the other coronavirus vaccines to roll out were slightly out of the orbit of Western Big Pharma, and may not have made as much of a contribution.

We already covered the second front on which COVID is being assaulted with the small molecule antivirals, but there was also progress attacking from a third direction, with new antibody therapeutics. After 2020 had seen the introduction of Regeneron's MAb combo REGEN-COV (casirivimab + imdevimab), AbCellera and Lilly's bamlanivimab, and Biocad's Ilsira (levilimab) for COVID complications, there was further activity last year in what became a fast-moving field. There were a further four products containing five novel NAS MAbs which left the runway during 2021. AstraZeneca was in the game again, with its combination product Evusheld (cilgavimab + tixagevimab) coming towards the end of the year, with subsequent data showing that it retained activity against the then newly discovered Omicron variant, which has since swept the world, visiting more countries than Michael Palin. No such luck for Eli Lilly though. Its 2020 monoclonal bamlanivimab was joined by etesevimab last year, and a combination product containing both agents was also launched. However, in January 2022, the US FDA withdrew the EUAs for both, along with those for the aforementioned REGEN-COV, as these monoclonals don't appear to be effective against Omicron. Rather than going on the trip of a lifetime, these drugs had little more than a long weekend away. There was similar bad luck for Celltrion's new anti-COVID MAb Regkirona (regdanvimab), which was launched just as Omicron emerged, and is believed to be less effective against that variant too. Celltrion is punching straight back by developing a combination of its agent with a new Omicron-sensitive MAb, CT-P63. But the final MAb against the coronavirus to be launched, GlaxoSmithKline's Xevudy (sotrovimab), looks like it will fare better, reportedly having less of a drop in antiviral potency than any of the other monoclonal antibodies developed thus far. In the world of anti-COVID MAbs, things move faster than a bullet train.

Away from the seemingly ubiquitous virus, there was also much to celebrate in terms of significant drug launches. Last year saw three more products added to the armoury of CAR-T therapeutics for use against cancer, effectively doubling the size of the CAR-T war chest. Two of these came via Bristol Myers Squibb. Abecma (idecabtagene vicleucel) entered the market for the treatment of relapsed or refractory multiple

myeloma, and encountered BMS country via its acquisition of Celgene. The company's other drug also came via BMS's shrewd M&A strategy, from its purchase of Juno Therapeutics. This was Breyanzi (lisocabtagene maraleucel), which debuted in the US for relapsed or refractory large B-cell lymphoma, including diffuse large B-cell lymphoma, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B. Proving that the West doesn't have a monopoly on exploring this exciting new territory, the third CAR-T was from China's JW Therapeutics: relma-cel (relmacabtagene autoleucel), which was also launched for large B-cell lymphoma.

Away from the twin peaks of COVID and cancer, there were additional interesting NASs for some rare metabolic syndromes, notably some biliary disorders. Both Albireo Pharma's Bylvay (odevixibat) and Mirum Pharmaceuticals' Livmarli (maralixibat) are ileal bile acid transport inhibitors, with the former approved for progressive familial intrahepatic cholestasis (PFIC), and the latter subsequently joining it on the US market for the related Alagille syndrome. Both are inherited genetic disorders. In PFIC, defects in biliary epithelial transporters cause a build-up of bile in liver cells, ultimately leading to liver failure and frequently death in childhood. In Alagille syndrome, a genetic defect causes bile duct paucity, which is characterised by narrow and malformed bile ducts. This similarly causes bile to build up in the liver, but also congenital heart problems. Mirum had originally intended to develop Livmarli for PFIC too, but, following Bylvay's approval, withdrew its EU application for PFIC and went for Alagille instead. An example of where the presence of other traffic on your route can cause you to change direction and head for a new destination.

Also within the city limits of rare metabolic disorders, we can visit Rhythm Pharmaceuticals' Imcivree (setmelanotide), a melanocortin (MC)-4 receptor agonist and melanocyte-stimulating hormone receptor agonist. This has been approved for a number of genetic disorders which produce reduced activation of the central MC-4 receptor, leading to early-onset severe obesity and pathological hunger. Thus far, the US FDA gave the go-ahead for prescription in proopiomelanocortin, proprotein convertase subtilisin/kexin type 1 or leptin receptor deficiency confirmed by genetic testing. Further obesity-related genetic disorders are in the pipeline, with a June 2022 PDUFA date scheduled for the additional indications of Bardet-Biedl syndrome and Alström syndrome. Rhythm took a leaf out of the oncology playbook in the development of this drug, conducting so-called 'basket' trials, whereby it used the same investigational regimen, but divided into separate subgroups based on different markers, providing a good way to study the different genetic variations of these inherited obesity syndromes.

Lastly in metabolic land, a riddle: when is a NAS not a NAS? That may sound like a dumb question, but it was one which the EMA and the makers of Nexviazyme (avalglucosidase alfa), Sanofi, certainly struggled to agree on. The drug is a modified version of the company's previously launched enzyme replacement therapy for Pompe disease, Myozyme (alglucosidase alfa), and the European agency believed that the newer drug could not be considered to be a new active substance because there was not enough difference between the two – effectively treating it like a prodrug (we ourselves don't count prodrugs as NASs if the active moiety has already been marketed). But Sanofi has argued that this approach is not appropriate for a biological, telling Pink Sheet "the CHMP NAS process applies a narrow interpretation of the NAS principles which is not appropriate for biological therapies and does not account for the innovative structural changes to enzyme replacement therapies, such as avalglucosidase alfa." The distinction is important because under EU legislation, NASs are awarded a

10-year exclusivity period (eight years of data exclusivity during which a generic competitor cannot reference the originator's data, plus an additional two-year exclusivity provision protecting against marketing of the generic). We have included the drug in our list of NASs for the year, but it does illustrate that the distinction may not always be as clear cut as you might think.

RNA therapeutics, while no longer exactly an undiscovered country, are still sufficiently outlying to merit a mention. As noted earlier, we have two in this batch. Leqvio, from the company with the biggest pipeline, Novartis (via its acquisition of The Medicines Company), is only the fourth RNA interference therapeutic to be successfully brought to the market. RNAi specialist Alnylam has been involved in all four, adding this drug to its portfolio comprising Onpattro (patisiran), Oxlumo (lumasiran), and Givlaari (givosiran). The new agent silences PCSK9, and is for use in the rare cardiovascular syndrome heterozygous familial hypercholesterolaemia. Similarly, Sarepta Therapeutics maintains its monopoly on antisense therapeutics using exon-skipping splice switching oligomers, with a third such launch in the form of Amondys 45, again for Duchenne muscular dystrophy. This one is for the exon 45 skipping version, and, like its predecessors Exondys 51 (eteplirsen) and Vyondys 53 (golodirsen), won accelerated approval from the US FDA based on the belief that an increase in dystrophin production is reasonably likely to predict clinical benefit, such as improved motor function. Confirmatory clinical trials are still underway.

Our final stop on our whistle-stop tour of interesting 2021 NASs – by which time we will have covered almost half of the set – is Verquvo (vericiguat). This Bayer and Merck & Co collaboration enters the crowded heart failure market in the US, but does have a specific, niche approved indication, namely, to reduce risk of cardiovascular death and heart failure rehospitalisation in patients with symptomatic chronic heart failure with reduced ejection fraction up to 45%, who have been hospitalised or need intravenous diuretic therapy.

With that, we complete our open-top bus tour of NAS city, having seen some of the most impressive sights which are truly a monument to the pharma industry's renaissance. I think we can all agree that this has been one of our best trips yet. As ever at the end of a holiday, one's thoughts immediately turn to the next one. Where will we go next year?

In a world beset by plagues and invasions, pharma continues to doggedly march to victory

Our globetrotting journey around the pharma R&D landscape and its landmark new active substances is now almost at an end. We've seen in this report that there were more new places of interest to visit this year than ever before, as the pharma industry emerges from two of years of a disruptive pandemic, blinking into the sunshine. It seems stronger than ever, having played an enormous role in helping tame the coronavirus and returning the world to some kind of normality.

It's sometimes difficult to remember that just a year ago, the vaccine roll-out was only really beginning to pick up speed. Twelve months later and most of us have had our three doses, with some moving on to a fourth. In the UK, all coronavirus-related restrictions were removed in February and things are, essentially, back to normal. Here, 92% of eligible people have received at least one vaccine dose, 85% two doses, and 67% a third. The speed with which the vaccines were developed, manufactured, and administered was nothing short of phenomenal. Of course there remains a significant challenge to deliver these kinds of results globally, with poorer countries still lagging behind, and as Omicron taught us, the world is not really out of the woods until vaccination levels reach these kinds of figures globally. But recent months have seen oral antivirals added to the armoury, so we really can have a fairly high degree of confidence that the pandemic phase of this infection is coming to an end. And pharma can take a huge amount of credit for this. It really did pull off a fantastic feat.

The ability of our species to turn triumph into disaster can never cease to amaze, however. Having just about got through two years of pandemic, which was probably self-inflicted to some extent if the coronavirus did indeed jump species due to illegal animal handling activities at that infamous Wuhan market, as I write in early March, the human race is now embarked on another colossal act of self-destruction, thanks to Russia's invasion of Ukraine. This appalling aggression from Putin's government has brought war to Europe on a scale not seen since 1945, and is precipitating a humanitarian disaster. This will once again disrupt the global economy, and pharma will not escape unaffected. Also, as Russia becomes a pariah state, a significant market and territory for clinical trials may all but disappear. At least Western pharma companies are rising to the challenge of supporting Ukraine, with many announcing large financial donations or gifts of free medicines. Let us hope that this madness has ended by the time you read this. I was lucky enough to have a city break in Kyiv only three years ago, and it is a wonderful city, with a rich cultural landscape. I look forward to the day when it resumes its status as a top tourist destination, not a warzone.

But while Ukraine may be off the holiday list for a while, prevailing conditions elsewhere seem encouraging. We've seen how China is exploding onto the global scene with a nascent pharmaceutical industry which is growing at such a rate that it is fast becoming a major power, and is now delivering its own homegrown new active substances. Might it single-handedly turbocharge pharma through the twenties and help it to navigate choppy waters elsewhere?

I think it's fair to say though, that as 2021 led the way in numbers of new NASs by a country mile, 2022 might struggle to keep up the pace. But what is just around the corner, and if pharma continues to run a tight ship, might we be in the same boat next year? There are certainly plenty of candidates heading for the departure lounge to board pharma airways flights this year. My colleague Alex Shimmings, Executive Editor, Commercial R&D for Scrip Intelligence, always gets her crystal ball out for us here, and selects a minibus-full list of drugs waiting in the wings to dazzle us with their beach bodies through the coming year; these can be seen in Table 3. The brochure includes some novel NASs which we fully expect to grace the pages of this report next year.

What became of our list of hotspots from last year's report? Well, eight of the nine we highlighted as potential cultural highlights did indeed make it onto our 2021 NAS list, giving us a much better hit rate than the 50% from the previous year. The only drug to go missing in action is Pfizer's atopic dermatitis therapy Cibinqo (abrocitinib), but this drug hasn't gone off the rails, as the company confirmed to us that it was expected to launch in February 2022. The remainder – Abecma, Aduhelm, Amondys 45, Bimzelx, Kerendia (finerenone), Lumakras, Nulibry, and Ukoniq – have mostly already been covered in this report due to novelty or other features of interest.

Whilst predictions are as likely to always come true as the weather is to be good on a UK staycation, plenty of industry commentators seem to be as excited about the coming years for pharma as at any other time in recent history. Top of many people's must-see attractions are forthcoming developments in oncology, and specifically immuno-oncology.

TABLE 3:
Selected important approvals/first launches expected in 2022

DRUG	COMPANY	INDICATION	NOTES
fezolinetant	Astellas	Menopause-related vasomotor symptoms	Oral neurokinin 3 receptor antagonist
lenacapavir	Gilead	HIV/AIDS	First-in-class; Complete response letter received
mosunetuzumab	Roche	Follicular lymphoma	Breakthrough therapy designation
oteseconazole	Mycovia Pharmaceuticals	Vulvovaginal candidiasis	First agent for the recurrent form
sutimlimab	Sanofi	Cold agglutinin disease	Approved Feb 2022
tebentafusp	Immunocore	Uveal melanoma	Approved Jan 2022
tirzepatide	Eli Lilly	Type 2 diabetes/obesity	First glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 co-agonist
zolbetuximab	Astellas	Gastric cancer	First-in-class

Source: Pharmaprojects/Scrip®, March 2022

Quoted in a recent article in our commercial insights publication, Scrip, Paul Peter Tak, president and CEO of Candel Therapeutics, noted that: "In recent years, we have noticed that it is possible to cure a patient with cancer using immunological intervention with immune checkpoint inhibitors. This breakthrough provides proof of concept for what may be achieved with immunotherapy. At the same time, most patients still exhibit an inadequate response to treatment. New approaches, such as oncolytic viral immunotherapies, may help to teach the patient's own immune system how to recognize and kill the tumor cells." Kevin Lee, CEO of Bicycle Therapeutics, struck a similar chord, commenting that: "Most exciting for me are the discoveries uncovering the potential for new agents to act as catalysts for the immune system – resetting the immune environment and amplifying the benefit patients can gain from checkpoint inhibitors. Enabling unresponsive patients, or those who are no longer responsive after initial treatment, to become responsive, would mean no cancer patient is left behind. That will be the next significant milestone in our immunotherapy research revolution."

Commentators are also suggesting that this decade could be the one where we crack some of the most perplexing conundrums which remain in neurological diseases. "Increased understanding of the complexity of the brain and its neurocircuitry will enable the industry to focus on novel targets and bring forward much-needed therapeutic options to treat Parkinson's disease, epilepsy, and schizophrenia," predicted Raymond Sanchez, chief medical officer at Cerevel Therapeutics. Maria Maccecchini, president and CEO of Annovis Bio, concurred, expecting "pivotal transformations to the neurodegenerative disease landscape" in 2022 and 2023, "including crucial data across the biotech and biopharma industries addressing Alzheimer's disease and Parkinson's disease."

Lastly, infectious diseases continued to be at the forefront of many experts' minds in the Scrip article, with COVID exerting both positive and negative influences. Some, such as Andy Smith of Equity Development, predicted that the bottom might fall out of the COVID-19 vaccine market, as oral antivirals move to become standard-of-care. Others noted that vaccination may only be part of the solution, with Michael Skynner, Bicycle Therapeutics' COO, pointing out that: "We have had SARS, SARS2, MERS, Zika, HIV and Ebola in recent memory and there will be others to come. Being ready and quick to mobilize solutions is the future, and small molecule treatments are going to be part of that toolbox." But the boost to new technologies which COVID accelerated led to sunny forecasts from other experts, with the chief medical officer of Moderna, Paul Burton, pointing out that "the last two years have shown the opportunity that mRNA vaccines represent." [For the full article on industry insiders' predictions on therapeutic area advances across the full spectrum of pharma R&D, visit https://scrip.pharmaintelligence.informa.com

So, despite everything which is going on in the world right now, we are completing our epic journey through pharma R&D country in an optimistic frame of mind. Invigorated by our international safari, we will have plenty of fond memories to cherish, and images to jog our memories. It's been an exhausting couple of years for everyone, and 2022 is already throwing up fresh challenges. But a holiday also always makes us appreciate more what we have at home too. It's now time to put away the sun lotion and contemplate a mountain of dirty washing, before climbing up the wooden hill to Bedfordshire to collapse tired but happy into the comfortable familiarity of our own bed. For pharma R&D in 2021–22 especially, but also for the entire past thirty years, it's been quite a trip. Pharmaprojects has enjoyed being your tour guide, and will continue to support your journeys through the pipeline landscape in the year ahead. So, what do you reckon? Same time next year?

ABOUT THE AUTHOR

Ian Lloyd
Senior Director,
Pharmaprojects & Data Integration

Ian Lloyd is the Senior Director of Pharmaprojects and Data Integration, overseeing the content and analyst services for our drug development solution. He supports clients in their drug pipeline data requirements and inquiries, providing insight into the best search strategies to answer their drug-related business questions and also identifying and analysing trends in pharma R&D. For the past 30 years, he has authored the "Pharma R&D Annual Review" and its new active substances (NAS) launches supplement. This has become a must-have industry report for those seeking to identify the changing fortunes of drug R&D. Ian joined Pharmaprojects in 1987, when it was part of PJB Publications. It was acquired by Informa in 2003. He previously worked in molecular biology as a research assistant at the University of Bristol.