PINK SHEET
CITELINE REGULATORY

20 Jan 2023 | **Analysis**

Orphans Account For More Than A Third Of EU New Drug Approvals In 2022

by Ian Schofield

Last year, the European Commission approved a record 55 therapies containing a new active substance, including 21 medicines for rare diseases. Among them were a number of gene therapies for indications such as cancer and hemophilia.

The number of medicines and vaccines containing a new active substance (NAS) approved in the EU hit a new high last year, with 55 products receiving a centralized marketing authorization, compared with 52 in 2021, which itself was a record number.

Orphan drug approvals also set a new benchmark in 2022, with 21 medicines for rare diseases accounting for more than a third of all NAS-containing products authorized for marketing by the European Commission. By contrast, 17 orphan approvals were granted in 2021.

Reflecting the growing role of advanced therapy medicinal products (ATMPs) in drug development, five gene therapies were approved in the EU in 2022, a significant rise on the two seen the previous year. Three of the therapies were for oncology indications, while one – *BioMarin Pharmaceutical Inc.*'s Roctavian (valoctocogene roxaparvovec) – became the first gene therapy to be approved for hemophilia A.

Four new vaccines passed muster in 2022, of which two – *Valneva SE*'s VLA2001 and *Sanofi*/*GSK plc*'s Vidprevtyn Beta – were for COVID-19. Two COVID-19 therapeutics were also granted approval – *AstraZeneca PLC*'s Evusheld (tixagevimab/cilgavimab) and *Pfizer Inc.*'s Paxlovid (nirmatrelvir/ritonavir). In 2021, seven COVID-19 products – four vaccines and three therapeutics – had been given the green light.

The data are based on information from the European Commission's database of EU drug approvals as of 19 January 2023, as well as on information from pharmaceutical companies and

Pink Sheet research.

Click here to explore this interactive content online

Exceptional Circumstances, Conditional Approvals

Seven products received EU approval under exceptional circumstances last year, all of them for orphan indications apart from *SIGA Technologies, Inc*'s Tecovirimat SIGA, which was authorized for treating mpox, smallpox and cowpox. Four products were approved in this way in 2021. Exceptional circumstances approvals are granted where there is no expectation that the company will be able to provide comprehensive efficacy and safety data, either because the condition is rare or because the collection of full data is impossible or unethical.

Conditional marketing authorization was granted to eight products in 2022, including Paxlovid – the only COVID-19 product to receive this kind of approval last year. This was a significant decline from 2021, when there were 14 conditional approvals (including the four COVID-19 vaccines). Conditional approvals can be granted on the basis of less comprehensive data than are normally required, with companies having to provide additional information post-authorization.

A full list of the EU NAS-containing product approvals in 2022 can be found in the *Pink Sheet*'s New EU Approvals *tracker*.

Oncology The Leading Category

As in 2021, oncology was the top therapeutic category in terms of new active substances last year, with 15 new drug approvals. As well as three of the gene therapies (see below), they included:

- *Novartis AG*'s Scemblix (asciminib) for chronic myeloid leukemia.
- Immucore's Kimmtrak (tebentafusp) for the treatment of human leukocyte antigen A*02:01 positive adult patients with unresectable or metastatic uveal melanoma.
- *Roche Holding AG*'s Lunsumio (mosunetuzumab), which received a conditional approval for the treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least two prior systemic therapies.
- *Bristol Myers Squibb Company*'s Opdualag (nivolumab/relatlimab) for the first-line treatment of advanced (unresectable or metastatic) melanoma.
- *Amgen, Inc.*'s Lumykras (sotorasib) for adults with advanced non-small cell lung cancer with a KRAS G12C mutation who have progressed after at least one prior line of systemic therapy.

- Zynlonta (loncastuximab tesirine) from *ADC Therapeutics SA* for relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma.

Other Areas

Approvals in other therapeutic areas included three products authorized for migraine (*Eli Lilly and Company*'s Rayvow (lasmiditan), *Biohaven Pharmaceutical Holding Company Ltd.*'s Vydura (rimegepant) and Lundbeck's Vyepti (eptinezumab).

There were two approvals each for anemia (Sanofi's Enjaymo (sutimlimab) and Global Blood Therapeutics' (now Pfizer's) Oxbryta (voxelotor)), lupus (*Otsuka Pharmaceutical Co. Ltd.*/*Aurinia Pharmaceuticals Inc.*'s Lupkynis (voclosporin) and AstraZeneca's Saphnelo (anifrolumab)), diabetes (Lilly's Mounjaro (tirzepatide) and *Bayer AG*'s Kerendia (finerenone)), and respiratory conditions (AstraZeneca's Beyfortus (nirsevimab) and AZ/Amgen's Tezspire (tezepelumab)).

Two orphan drugs received approval for growth hormone deficiencies: Pfizer's Ngenla (somatrogon) and *Ascendis Pharma A/S*'s lonapegsomatropin Ascendis Pharma (which has since been renamed Skytrofa).

Click here to explore this interactive content online

The New Gene Therapies

The more than doubling of the number of gene therapy approvals compared with 2021 was testament to the growing contribution of ATMPs to the therapeutic arsenal as more individualized, one-off treatments come through company pipelines. As well as gene therapies, ATMPs include somatic-cell therapy medicinal products and tissue-engineered products.

BioMarin's Roctavian

BioMarin's Roctavian, which has orphan status and was the first gene therapy to be OKd for hemophilia, received a conditional approval in August for the treatment of severe hemophilia A.

BioMarin said that valoctocogene roxaparvovec works by delivering a functional gene that is designed to enable the body to produce Factor VIII on its own without the need for continued hemophilia prophylaxis, "thus relieving patients of their treatment burden relative to currently available therapies."

Roctavian has not fared so well in the US, though. An initial rejection of the biologics license application (BLA) by the Food and Drug Administration in August 2020 was followed by an FDA request for more follow-up data, which pushed back the resubmission by more than two years. Moreover, in November last year BioMarin said the BLA could face a further delay, this time of

three months, to the expected FDA action date of 31 March 2023, in order to give the agency more time to review additional data from a three-year analysis of the company's GENEr8-1 study. (Also see "*BioMarin Prepares Investors For A Possible US Hemophilia Gene Therapy Delay*" - Scrip, 8 Nov, 2022.)

Atara's Ebvallo

Another gene therapy breakthrough last year was *Atara Biotherapeutics, Inc.*'s orphan product Ebvallo (tabelecleucel), the first monotherapy for the treatment of adult and paediatric patients two years of age and older with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) who have received at least one prior therapy.

Recommending the product's approval last year, the European Medicines Agency said Ebvallo, which was approved under exceptional circumstances, produced "clinically significant responses (complete or partial) in around half of patients involved in the main study." These results were "considered promising in a setting where patients generally have a very poor prognosis and limited treatment options," it added.

PTC's Upstaza

The third gene therapy is Upstaza (eladocagene exuparvovec) from *PTC Therapeutics, Inc.*, which was approved for the treatment of patients aged 18 months and older with a clinical, molecular, and genetically confirmed diagnosis of aromatic L amino acid decarboxylase deficiency with a severe phenotype. It too is an orphan therapy with an exceptional circumstances approval.

Janssen's Carvykti

Janssen Pharmaceutica Inc.'s Carvykti (ciltacabtagene autoleucel, or cilta-cel), which also has EU orphan status, is a gene therapy for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy.

The EMA said that a single infusion of Carvykti, which has a conditional marketing authorization, led to "clinically meaningful responses rates in multiple myeloma patients whose cancer had come back and did not respond to previous treatments."

BMS's Breyanzi

Bristol Myers Squibb's Breyanzi (lisocabtagene maraleucel) – the only gene therapy without orphan status – was approved for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma and follicular lymphoma grade 3B, after two or more lines of systemic therapy.

Click here to explore this interactive content online

Orphan Drugs

Among other orphan therapies approved in the EU last year were:

- *Mirum Pharmaceuticals, Inc.*'s Livmarli (maralixibat chloride), which received an exceptional circumstances approval for the treatment of cholestatic pruritus in patients with Alagille syndrome aged two months and older.

- *Eiger BioPharmaceuticals, Inc.*'s Zokinvy (lonafarnib), which also received an exceptional circumstances approval, for the treatment of patients 12 months of age and older with a genetically confirmed diagnosis of Hutchinson-Gilford progeria syndrome or a processing-deficient progeroid laminopathy.

- Amvuttra (vutrisiran), from *Alnylam Pharmaceuticals Inc.*, for the treatment of hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.

- *BridgeBio Pharma, Inc.*/*Sentynl Therapeutics, Inc.*'s Nulibry (fosdenopterin) for the treatment of patients with molybdenum cofactor deficiency Type A (approval under exceptional circumstances).

- Sanofi's Xenpozyme (olipudase alfa), an enzyme replacement therapy for the treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency.

- *argenx*'s Vyvgart (efgartigimod alfa) as an add on to standard therapy for adult patients with generalized myasthenia gravis who are anti-acetylcholine receptor antibody positive.

One Diagnostic

One diagnostic medicine was approved under the EU centralized procedure last year: Novartis's Locametz (gozetotide) for the detection of prostate-specific membrane antigen-positive lesions.