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EU Gene Therapy Submissions, Approvals Expected To Pick Up In 2021

by Amanda Micklus

Coming year could feature first-time approvals in the EU for at least five gene therapies.

First-time approvals of gene therapies globally were relatively low in 2020, but activity of this market in the EU could increase the total greatly in 2021, based on an analysis of anticipated marketing authorization application submissions and approval decisions.

The coming year could feature first-time approvals in the EU for at least five gene therapies, and regulatory submissions for at least another three *(see chart)*.

In 2020, some expected submissions were delayed due to the impact of COVID-19, while others faced manufacturing and clinical trial hurdles. Still, the industry saw two first-time approvals worldwide in this class (which for purposes of this analysis only include directly administered gene therapies and gene-modified cell therapies, and exclude cell therapies that are not genetically modified). In July, the US Food and Drug Administration approved *Gilead Sciences, Inc.*'s Tecartus (brexucabtagene autoleucel), a CAR-T therapy for relapsed or refractory mantle cell lymphoma. (Also see "*Keeping Track: Kite's Tecartus Is Third CAR-T With US FDA Approval; Submissions Round-Up*" - Pink Sheet, 26 Jul, 2020.) And in December, just before year end, the European Commission granted full market authorization to *Orchard Therapeutics Limited*'s Libmeldy (autologous CD34+ cells encoding the ARSA gene) for metachromatic leukodystrophy. *((Also see "European CHMP Opinions and MAA Updates*" - Pink Sheet, 21 Dec, 2020.))

The gene therapy class did, however, drop by one product in 2020 with Orchard halting treatment in the EU with Strimvelis (autologous CD34+ enriched cells) after a case of lymphoid T-cell lymphoma was disclosed in a patient who received the therapy in 2016. The company is investigating the case, but believes it might be related to insertional oncogenesis. Strimvelis had been approved for adenosine deaminase deficiency and has only been given to 16 patients to date. The Strimvelis news came almost one year after another gene therapy was pulled from the

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EU market: Molmed's (*AGC Biologics S.p.A.*) Zalmoxis held conditional marketing authorization, but that was withdrawn in October 2019 when an interim analysis of the Phase III TK008 trial showed no advantage for Zalmoxis over standard of care in against the primary endpoint. (Also see "*Disappointing End For MolMed's Zalmoxis Cell Therapy In EU*" - Pink Sheet, 11 Oct, 2019.)

According to Pharmaprojects, there are now currently 14 approved gene therapies globally, including Libmeldy and Strimvelis.

That number could increase in 2021 thanks to an uptick in EU regulatory activity. *bluebird bio* may see two of the anticipated approvals.

Lenti-D (elivaldogene autotemcel), an ex vivo genetically modified cell therapy for cerebral adrenoleukodystrophy, could become the company's second gene therapy approval after Zynteglo (betibeglogene autotemcel; autologous CD34+ cells encoding $^{\beta A\text{-}T87Q}$-globin gene) gained conditional marketing authorization in June 2019. In mid-2021, bluebird also plans to submit Lenti-D in the US. Another bluebird bio asset, the CAR-T idecabtagene vicleucel partnered with *Bristol Myers Squibb Company*, could be cleared in the EU. The European Medicines Agency is reviewing ide-cel, which targets BCMA for multiple myeloma, under accelerated assessment.*

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By Bridget Silverman

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Another BMS therapy – lisocabtagene maraleucel (liso-cel), from subsidiary Celgene for the treatment of relapsed/refractory diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and follicular lymphoma grade 3B – initially had accelerated assessment status at the EMA. However, the review is now being undertaken via a standard timeline for undisclosed reasons, potentially pushing out approval by a few months. *(Also see "Fast-Track Loss In EU For Celgene's CAR-T Cell Therapy*" - Pink Sheet, 18 Dec, 2020.)

Also of note in the EU is the expected resubmission of *BioMarin Pharmaceutical Inc.*'s MAA for Roctavian (valoctocogene roxaparvovec) in the second quarter of 2021. (Also see "*BioMarin Pulls EU Hemophilia Gene Therapy Filing, But Is Not Giving Up*" - Pink Sheet, 16 Nov, 2020.) In a September

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2020 US Securities and Exchange Commission filing, BioMarin disclosed that the EMA requested full 52-week data from 134 patients in the company's Phase III trial in the 6e13 vg/kg dose. BioMarin ended up withdrawing the MAA in November 2020. It faced a similar issue in the US, where it received a complete response letter in August 2020, with the FDA requiring two-year follow-up date on the advanced bleed rate durability from the Phase III 270-301 study. (Also see "*Not Such A Sure Thing: FDA Knocks Back BioMarin's Roctavian*" - Pink Sheet, 19 Aug, 2020.)

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While an uptick in gene therapy approvals will be welcome to patients who are in dire need of treatments with little to no other options, the key question in EU countries will be around pricing and market access. Existing gene therapies on the market that are one-time treatments have been funded through alternative payment models, but payers are looking closely at the clinical data, especially durability, to back up these therapies and basing funding arrangements around that evidence. Further, there is uncertainty around the supply chain due to COVID-19, especially cold chain supply capacity required and potentially reallocated toward certain vaccines, such as mRNA, and away from cell therapies that also require cryopreservation and are shipped to centralized locations – including across EU borders – for genetic engineering.

The US similarly is expected to see a revitalization in gene therapy regulatory submissions in 2021. Several of the companies planning submissions are also expected to submit or have submitted BLAs in the US. *(See sidebar. above.)* At the Alliance for Regenerative Medicine's annual Meeting on the Mesa in October 2020, Peter Marks, the director of FDA's Center for Biologics Evaluation and Research, said that cell and gene therapy IND applications in 2020 were on track to exceed the 250 INDs received in 2019. He also predicted 40 to 60 product launches and over 500,000 patients treated by 2030.

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Following a positive marketing recommendation from the EMA, the European Commission has 67 days in which to issue formal pan-EU marketing approval.

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**This section and the following were updated on 9 February 2021 to reflect the fact that the original*

article confused idecabtagene vicleucel (ide-cel) with lisocabtagene maraleucel (liso-cel) Ide-cel is in fact still being reviewed under the EMA's accelerated assessment mechanism. Liso-cel is not.