European Approval Process Coverage
Winners & Losers: A Deep-Dive Into The EMA's PRIME Scheme

Executive Summary
Nine of the 70 medicines for unmet medical needs that have to date won a place on the European Medicines Agency’s PRIME scheme are now approved for sale in the EU, and two more approvals are expected soon. Meanwhile, most applications for a “priority medicine” designation are still missing the mark.

Drug developers are continuing to show a lot of interest in the European Medicines Agency’s priority medicines (PRIME) scheme and the advantages it offers.

Since the scheme was launched in 2016, the EMA has received over 300 applications from companies seeking a PRIME designation for their early-stage investigational products. The aim of the program is to get drugs for unmet medical needs to patients faster by helping developers optimize their development plans and increasing the likelihood of having their products fast-tracked when they are eventually filed for regulatory review.

Almost half of the medicines that have been accepted onto scheme have been advanced therapy medicinal products (ATMPs). PRIME-designated products cover a wide range of therapeutic areas – with oncology and hematology medicines making up the largest share. Most are being, or have been, developed almost equally by small and medium-sized enterprises (SMEs) and bigger pharma companies.

To date, nine products that were awarded PRIME designation have gone on to win pan-EU marketing approval, including Europe’s first two CAR T-cell based treatments and some cutting-edge gene therapies.

In this article, the Pink Sheet explores how PRIME has been faring in the four years it has been operating.

Optimizing Development Plans
Developers of products that win a place on the scheme are offered enhanced support from the EMA to help them optimize their development plans and they may also secure review under the agency’s accelerated assessment mechanism when they file the marketing application for their product for evaluation.

The scheme has tough eligibility criteria. Applicants must convince the EMA that their investigational product has the potential to benefit patients with an unmet medical need, based on early clinical data.

As of late July 2020, the EMA had received 308 applications for entry onto PRIME. Of the applications reviewed, 70 have won PRIME designation and 228 were turned down. Ten applications were discarded and not reviewed.

Crossing The Finishing Line
Nine PRIME-designated products have so far received pan-EU marketing approval. These include the CAR T-cell cancer therapies Kymriah and Yescarta, and the gene therapies Zyn前台 and Zolgensma for treating transfusion-dependent β-thalassemia and spinal muscular atrophy respectively. The table below lists the nine products that have been approved.
Six of the nine medicines were granted a conditional marketing authorization, which means the companies are required to provide the EMA with more data post-approval. The products in question are: Rozlytrek, Hepcludex, Zynteglo, Zolgensma, Ervebo and Polivy.

### Oncology And Hematology Are The Winners
The applications that have been accepted onto the scheme cover a wide range of therapeutic areas, with oncology and hematology medicines making up the largest share. Nineteen of the 70 PRIME-designated drugs are for cancer and 13 are for treating hematology/hemostaseology conditions, accounting respectively for 27% and 19% of the total. Only five of the 32 applications targeting neurology have been accepted as have just two of the 18 applications for cardiovascular diseases. See bar char below for all the therapeutic areas in the applications.

Some 47% (33 products) of products accepted onto the scheme have been ATMPs. The EMA has previously observed that a large proportion of ATMPs are being developed by SMEs who often lack experience of the regulatory approval process.

---

### PRIME-Designated Products Approved In The EU As Of 17 August 2020

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rozlytrek (entrectinib)</td>
<td>Roche</td>
<td>For the treatment of people with NTRK fusion-positive solid tumors and for people with ROS1-positive advanced non-small cell lung cancer</td>
</tr>
<tr>
<td>Hepcludex (bulevirtide)</td>
<td>MYR Pharmaceuticals</td>
<td>For the treatment for chronic hepatitis delta virus infection and compensated liver disease</td>
</tr>
<tr>
<td>Zynteglo (autologous CD34+ cells encoding βA-T87Q-globin gene)</td>
<td>bluebird bio</td>
<td>Gene therapy for transfusion-dependent β-thalassemia</td>
</tr>
<tr>
<td>Givlaari (givosiran)</td>
<td>Alnylam Pharmaceuticals</td>
<td>RNAI therapeutic for treating acute hepatic porphyria in adults and adolescents</td>
</tr>
<tr>
<td>Zolgensma (onasemnogene abeparvovec)</td>
<td>AveXis/Novartis</td>
<td>Gene therapy for spinal muscular atrophy</td>
</tr>
<tr>
<td>Ervebo (rVSVΔG-ZEBOV-GP, live)</td>
<td>MSD</td>
<td>Vaccine for Ebola virus disease caused by Zaire Ebola virus</td>
</tr>
<tr>
<td>Polivy (polatuzumab vedotin)</td>
<td>Roche</td>
<td>For use in combination with bendamustine plus MabThera (rituximab) for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma who are not candidates for a hematopoietic stem cell transplant.</td>
</tr>
<tr>
<td>Kymriah (tisagenlecleucel)</td>
<td>Novartis</td>
<td>CAR T-cell therapy for the treatment of pediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukemia that is refractory, in relapse post-transplant or in second or later relapse, and for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy</td>
</tr>
<tr>
<td>Yescarta (axicabtagene ciloleucel)</td>
<td>Kite</td>
<td>CAR T-cell therapy for treating adult patients with relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma, after two or more lines of systemic therapy</td>
</tr>
</tbody>
</table>
Regarding the remaining product types, 19 are small molecules (which the EMA refers to as chemicals), 15 are biologicals and three are immunological drugs.

While PRIME-designated products are being – or have been – developed almost equally by SMEs and bigger pharma companies, there have been a handful of applications from academia, but these have all been turned down.

Ten of the 308 applications were discarded without having been reviewed because they were deemed to be outside the scope of the scheme or to have a format and content inadequate to support their review.

No Guarantees
Five PRIME-designations have been withdrawn at the request of the companies involved, mostly because they had discontinued development. Withdrawal from the scheme does not necessarily spell the end of the road for a product.

Aducanumab
For example, aducanumab, Biogen and Eisai’s investigational drug for treating Alzheimer’s disease was among the first products to win a PRIME designation. The anti-amyloid agent was later withdrawn from the scheme after producing poor results in Phase III trials. These results were announced in May 2019 and the companies said they were discontinuing Phase III trials. A few months later, Biogen surprised everyone by saying that a further analysis of the trial data had shown positive results and plans to pursue regulatory approval for the product were on again. In July 2020, the company said it had completed the submission of a biologics license application (BLA) to the US Food and Drug Administration for the approval of aducanumab and that it “has continued to engage in dialogue with regulatory authorities in other markets, including Europe and Japan, working diligently toward the goal of submitting applications in these markets.” (Also see “Adu-CAN-umab? Reading The Tea Leaves For Biogen’s US Filing For Alzheimer’s Drug” - Pink Sheet, 10 Aug, 2020.)

Vocimagene Amiretrorepvec
Another product withdrawn from the scheme was Tocagen’s gene therapy for high-grade glioma (HGG), Toca 511 (vocimagene amiretrorepvec). The company’s Toca 511/Toca FC treatment last year missed the primary endpoint of overall survival compared to standard of care treatment and all secondary endpoints in a Phase III trial. Tocagen has since merged with dermatology firm Forte Biosciences, but a statement from the latter in June does not mention any future plans for the HGG treatment.

Emapalumab
Getting on and staying on the scheme also does not necessarily guarantee EU marketing approval. Gamifant (emapalumab), from Swedish Orphan Biovitrum (Sobi), received PRIME designation in May 2016 and a marketing authorization application (MAA) for the product was submitted to the EMA for review in September 2018. Having reviewed the MAA, the agency last month recommended against approving the potential treatment for primary hemophagocytic lymphohistiocytosis. Sobi, which has already received US approval for Gamifant, said it would appeal against the EMA’s decision. (Also see “Sobi To Appeal Against EMA Rejection For Emapalumab” - Pink Sheet, 24 Jul, 2020.)

Two More Approvals In The Wings
Another two PRIME-designated products are expected to be approved soon – GlaxoSmithKline’s multiple myeloma drug, Blenrep (belantamab mafodotin), and Hansa Biopharma’s Idefirix (imlifidase), for the desensitization of highly sensitized patients who need kidney transplantation but are unlikely to receive a compatible transplant. The EMA recommended
that Blenrep and Idefirix be granted EU marketing approval in July and June respectively. The agency’s recommendations are sent to the European Commission, which usually takes around two months to issue a formal approval.

The Fate Of PRIME Applications

- PRIME applications not reviewed & discarded: 10
- PRIME designations awarded: 70
- PRIME applications denied: 228
PRIME Applications By Therapeutic Area As Of 23 July 2020*

EGFM - Endocrinology-gynecology-fertility-metabolism; IRT - Immunology-rheumatology-transplantation; NPIC - Neonatology-pediatric intensive care.

*Out of scope applications are not included in this chart.

Source: EMA
This Year
There is continuing interest in PRIME.

In 2020 to date, the EMA has reviewed a similar number of applications for PRIME compared with the same period last year.

Between January and the end of July this year, the agency reviewed 34 applications versus 30 applications in the first seven months of 2019. Six investigational drugs have made it onto the scheme this year, compared with seven during the same time period in 2019, a year that culminated in 16 PRIME designations being granted.

The rejection rates for the applications in the first seven months of 2020 and 2019 are also similar, at 82% (28 applications denied) and 76% (23 denied) respectively.

The latest investigational drugs to receive PRIME designation are Adaptimmune Therapeutics’ ADP-A2M4 cell therapy for synovial sarcoma and Imago BioSciences’ myelofibrosis treatment, bomedemstat.

The applications from the two companies were among seven such requests that the EMA reviewed in July – the other five failed to make the grade. The table below lists all the products that have made it onto the scheme this year.

### Products Granted PRIME Designation In Jan-July 2020

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viralym-M</td>
<td>AlloVir</td>
<td>Allogeneic, off-the-shelf, multi-virus specific T-cell therapy</td>
</tr>
<tr>
<td>PB2452</td>
<td>PhaseBio Pharmaceuticals</td>
<td>For reversing the antiplatelet effects of ticagrelor in patients with uncontrolled major or life-threatening bleeding or requiring urgent surgery or invasive procedure</td>
</tr>
<tr>
<td>AAV-RPGR</td>
<td>Janssen/MeiraGTx</td>
<td>Gene therapy for X-linked retinitis pigmentosa</td>
</tr>
<tr>
<td>Sotatercept</td>
<td>Aceleron Pharma</td>
<td>For treating pulmonary arterial hypertension</td>
</tr>
<tr>
<td>ADP-A2M4</td>
<td>Adaptimmune Therapeutics</td>
<td>Cell therapy for synovial sarcoma</td>
</tr>
<tr>
<td>Bomedemstat</td>
<td>Imago BioSciences</td>
<td>For the treatment of myelofibrosis</td>
</tr>
</tbody>
</table>

### Most Applications Denied

PRIME’s high rejection rate is perhaps to be expected. As noted by the EMA in its 2019 annual report, published in June 2020, the scheme is intended for only the most promising medicines and the agency focuses its attention on products that have the potential to bring a major therapeutic advantage.

As such, the entry criteria are strict. Applicants must demonstrate that their investigational product has the potential to benefit patients with an unmet medical need, based on early clinical data.

For example, Adaptimmune’s ADP-A2M4 was accepted based on clinical data from a Phase I trial, which the company said demonstrated “compelling efficacy and early promising durability, with tolerable safety in patients with synovial sarcoma.” Based on these data, Adaptimmune initiated its Phase II SPEARHEAD-1 trial of ADP-A2M4, enrolling patients with advanced synovial sarcoma and myxoid/round cell liposarcoma at clinical sites in Canada, France, Spain, the UK, and the US.
For Imago’s application, the EMA reviewed non-clinical and clinical data for bomedemstat (IMG-7289) from the ongoing Phase II study, which the company said demonstrated improvements in symptom scores, spleen volumes, anemia and bone marrow fibrosis. Bomedemstat works by inhibiting lysine-specific demethylase 1 (LSD1 or KDM1A), an enzyme shown to be essential for maturation of blood cells and vital to neoplastic stem/progenitor bone marrow cells. The company last month said its Phase IIb study of the product was actively enrolling in the EU, the US and the UK.

The five applications that were rejected in July relate to an investigational influenza vaccine and treatments for non-arteritic retinal artery occlusion, X-linked retinitis pigmentosa, septic shock, and newly diagnosed multiple myeloma patients who have undergone autologous stem cell transplantation.

The EMA has previously explained why applications fail to make the grade. (Also see “Why Four In Five Applications For PRIME Still Fail Two Years On: EMA Clarifies Expectations” - Pink Sheet, 11 May, 2018.) As noted by industry in the past, a great deal of preparation is required when it comes to putting together an application for entry to the scheme.

The fact that a medicine is not accepted in PRIME does not mean that its development should not be pursued. As previously noted by the agency, “medicines that are not granted PRIME access can still benefit patients by providing alternative treatment options for a disease.”

State Of Play In 2019
PRIME’s popularity and the fate of applications seeking designation were highlighted in the EMA’s 2019 annual report.

According to the report, the agency last year reviewed a total of 57 applications; it accepted 16 and rejected the rest.

The rate of products granted access to the scheme was slightly higher in 2019 compared with 2018, at 28% last year compared with 23% in 2018, when 14 of the 59 applications reviewed were accepted.

The report observes that “2018 and 2019 showed stable numbers in eligibility requests, after the peak in 2017 that followed the launch of the scheme.” It notes that of the 81 applications reviewed in 2017, 19 were granted and 62 were denied. And in 2016, 15 of the 67 applications reviewed were accepted. See following bar chart.
PRIME Versus US BTD

PRIME is similar to the breakthrough therapy designation (BTD) scheme that the US Food and Drug Administration operates. BTD is designed to expedite the development and review of drugs that are intended to treat a serious condition and for which preliminary clinical evidence indicates may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).

A number of products on the PRIME scheme have also received BTD designation.

Last year, the EMA published a report on a workshop it held with the FDA about their early access mechanisms such as PRIME and BTD. (Also see “Regulators, Industry Agree That Frequent Communication Is Key In Developing Breakthrough, PRIME Therapies “ - Pink Sheet, 1 Aug, 2019.) A major difference between the EU and the US schemes is that PRIME is only available for one indication per product whereas BTD is available for multiple indications.
EU Accelerated Assessment – Hard To Get, Hard To Keep

Executive Summary
It’s hard enough in the first place for companies to persuade the European Medicines Agency that their planned marketing authorization application should be fast-tracked. Many are also finding that after accelerated assessment is granted, it is taken away during the actual review.

Many of the marketing authorization applications (MAAs) that until recently were being evaluated under the European Medicines Agency’s accelerated assessment mechanism have reverted to standard review timelines. The MAAs relate to products such as AveXis’s gene therapy, Zolgensma, and several other products that, like Zolgensma, have already been approved in the US.

Seven MAAs that were originally granted accelerated assessment and were initially being processed under this mechanism are no longer undergoing speedy review, according to the latest monthly list of products being reviewed under Europe’s centralized evaluation procedure at the EMA.

It appears that just four MAAs are currently being fast-tracked.

Fast-track review in the EU is reserved for products that are expected to be of major public health interest, particularly from the point of view of therapeutic innovation. The mechanism reduces the time it takes the EMA to evaluate an MAA from 210 days to 150 days (not counting clock stops when applicants have to provide additional information). Fast-track requests should be made at least two to three months before the MAA is submitted.

Around half the requests companies make to the EMA for accelerated assessment are rejected. In 2019 to date, just three out of the nine requests processed have been granted.

The seven MAAs that have reverted to standard review relate to the following products:
• Shionogi’s investigational antibiotic agent, cefiderocol.
• Stemline Therapeutics’ tagraxofusp (Elzonris) for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN), a rare blood cancer.
• Onasemnogene abeparvovec/AVXS-101 (Zolgensma), the gene replacement therapy from Novartis/AveXis for the treatment of spinal muscular atrophy (SMA).
• Theratechnologies/TaiMed Biologics’ new HIV therapy, ibalizumab (Trogarzo).
• Daiichi Sankyo Europe’s acute myeloid leukemia (AML) therapy, quizartinib (Vanflyta).
• Karyopharm Therapeutics’ multiple myeloma drug, selinexor (Xpovio).
• The tissue-agnostic cancer treatment, larotrectinib (Vitrakvi), from Bayer/Loxo Oncology.

Some of the products have been approved elsewhere but there have often been problems along the way. One product – Daiichi Sankyo’s AML therapy, quizartinib – was approved in Japan but rejected in the US.

Importance Of Robust Data
Asked to comment on the high number of switches from accelerated to standard review, the EMA said it was important to note that marketing applications should be mature in terms of the data submitted at the start of the evaluation.

The agency further noted: “Requests for accelerated assessment are voluntarily made by
the applicants and should be duly substantiated. In order to meet the short timelines of the assessment, applicants are strongly advised to enter [in timely manner] in a dialogue with the EMA to prepare for an evaluation under accelerated assessment.”

In at least three of the cases in hand, a scientific advisory group was or will be convened by EMA’s reviewing committee, the CHMP, as part of the assessment of the MAA.

**The Companies Explain**
The Pink Sheet contacted all the companies involved for comment. Six replied, providing various levels of detail. Only Stemline did not respond.

**AveXis And Zolgensma**
With regard to Zolgensma, AveXis Inc. said that being on a standard approval timeline would “give the [EMA] the time they need to review the robust amount of data we are providing to answer their questions.”

It added that it continued to work closely with European regulators during their review of its product and that it was anticipating a potential approval in the second half of 2019.

According to Kacper Rucinski, a London-based executive board member of the nonprofit group SMA Europe, the EMA “has quite a significant number of questions for AveXis”. He added: “My understanding is that the EMA wants to very thoroughly review the data and the scope of approval.”

Zolgensma was approved in the US for all three types of SMA at the end of May. (Also see “Novartis CEO Calms Concerns Over Zolgensma launch “ - Scrip, 18 Jul, 2019.) There is considerable interest over what is happening in Europe, where, even if Zolgensma is approved, there will be a struggle to get individual countries to agree to cover the $2m treatment.

Of the seven products whose accelerated review has reverted to standard timelines, Zolgensma is the only one receiving support under PRIME, the EMA’s priority medicines scheme. Products in PRIME are expected to undergo accelerated assessment.

**Karyopharm And Selinexor**
Karyopharm told the Pink Sheet that it submitted its MAA to the EMA in January requesting conditional approval for selinexor, in combination with dexamethasone, as a new treatment for patients based on the results of the Phase 2b STORM study in patients with triple class refractory multiple myeloma who were previously exposed to all five of the most commonly prescribed anti-myeloma therapies currently available.

The company said: “As a customary part of the marketing application review process, Karyopharm received the consolidated list of questions from EMA in early May 2019 and anticipates receiving additional feedback based on routine site audits and other activities. To provide adequate time to evaluate the application and allow Karyopharm to respond to questions and feedback, the EMA has switched from an accelerated review to a traditional review. We expect to receive a decision on the application by the end of 2019.”

Selinexor was approved as Xpovio in the US on 3 July with an accelerated approval, despite a Food and Drug Administration advisory panel having said that approval should be delayed until results of the randomized Phase III BOSTON trial were available. Full top-line results from BOSTON are not expected until the end of the year. (Also see “Karyopharm Selinexor Approval Likely Awaits BOSTON Trial, But US FDA Promises To Move
Theratechnologies/TaiMed And Ibalizumab
Theratechnologies said that the MAA for it and TaiMed’s ibalizumab was switched to a standard procedure when the CHMP requested a scientific advisory group for its application. This “delayed the review slightly,” Theratechnologies Inc. added. The CHMP aimed to convene its scientific advisory group for HIV/viral diseases in early April. Theratechnologies said in a statement in late May that it had requested and obtained from the EMA an additional month to address new questions it had received in regard to the establishment of a post-approval registry to gather long-term data on patients taking ibalizumab in Europe.

The company said at that time that it would submit responses to the EMA by the end of June, after which the CHMP would then have 30 days to provide a recommendation on whether ibalizumab should be approved in Europe. “Assuming a positive CHMP opinion, our plans to launch in Germany before the end of the year remain unchanged,” it said. The timelines cited by Theratechnologies suggest that ibalizumab should be among the MAAs up for an opinion from the CHMP at its next monthly meeting, which takes place on 23-25 July.

Approved in the US in early 2018, ibalizumab/Trogarzo was the first HIV therapy with a new mechanism of action to reach the market in 10 years.

Daiichi Sankyo’s Quizartinib
Daiichi Sankyo confirmed that the CHMP had determined that the standard review period would be required to review the MAA for quizartinib. It added that it was “not uncommon” for MAAs to revert to the standard review timeline during the EMA’s review process.

In the US, the FDA issued Daiichi Sankyo with a complete response letter for quizartinib in June this year, just days after it secured its first approval - in Japan, as Vanflyta. An FDA advisory committee had voted 8-3 against an approval in mid-May, after questions over persuasive evidence of efficacy. (Also see “Keeping Track: FDA OKs AMAG’s Vyleesee, But Bronchitol And Quizartinib Draw CRLs” - Pink Sheet, 21 Jun, 2019.) (Also see “AML Contender Quizartinib Draw CRLs” - Pink Sheet, 21 Jun, 2019.)

Bayer/Loxo And Larotrectinib
Regarding the status of the MAA at the EMA for Loxo Oncology and Bayer AG’s larotrectinib, Bayer said only that it was currently in discussions with the regulatory authorities, that it could not share details from those discussions, and that it would provide updates as they became available.

Bayer and Loxo (now owned by Eli Lilly) are jointly developing larotrectinib. They are seeking approval in the treatment of adult and pediatric patients with locally advanced or metastatic solid tumors (excluding primary central nervous system tumors) with a neurotrophic tyrosine receptor kinase (NTRK) gene fusion after prior standard therapy or as initial therapy when there is no adequate treatment option.

In November 2018, larotrectinib was approved in the US, where it is marketed as Vitrakvi. (Also see “Vitrakvi, Daurismo Approvals Put US FDA On Brink Of Another Record “ - Pink Sheet, 27 Nov, 2018.)

Shionogi And Cefiderocol
Like Daiichi Sankyo, Shionogi chose to point out that it was not unusual for accelerated assessments to revert back to standard review. “This is reflective of the complexity within
Shionogi was granted accelerated assessment for two separate planned MAAs involving cefiderocol. One covered the treatment of infections caused by carbapenem-resistant gram-negative bacteria in adults with limited treatment options and the other covered treatment of infections caused by aerobic gram-negative bacteria in adults with limited treatment options.

The MAA under review is for the latter indication, which, Shionogi pointed out, is “the more extensive of the two”. This label incorporates the other indication, it said.

Cefiderocol has yet to be approved in any market, according to Informa’s Biomedtracker.

**Stemline And Tagraxofusp**

Stemline Therapeutics is seeking approval of its CD123-directed cytotoxin tagraxofusp for the treatment of adult and pediatric patients, two years or older, with BPDCN.

The company noted earlier this month that the tagraxofusp MAA review would proceed on a standard timeline and that it expected the CHMP to issue an opinion later this year on whether the product should be approved for marketing in the EU. A scientific advisory group meeting is planned for September as part of the review.

If its MAA is successful, Stemline is targeting a commercial launch in Europe in the first quarter of 2020. In the meantime, the company continues “to build out a European commercial infrastructure in advance of potential approval.

Tagraxofusp was approved in the US in December 2018, achieving one of the fastest novel product review times of the year, at exactly six months. (Also see “Keeping Track Of The US FDA’s Final Approvals Of 2018” - Pink Sheet, 2 Jan, 2019.) Marketed as Elzonris, it was the first drug to be approved for BPDCN in the US, where it has the following black box warning: “Capillary Leak Syndrome (CLS), which may be life threatening or fatal if not properly managed, can occur in patients receiving Elzonris.”

**Trackers**

The EMA told the Pink Sheet that it only began proactively identifying products no longer being reviewed under the accelerated assessment program in June. The aim is to increase transparency and clarity about the procedure, it said.

The status of all MAAs granted accelerated assessment since the beginning of 2018 is recorded in the table below. For details of the outcome of all fast-track requests made in 2018 and in 2019 to date, see the latest edition of the Pink Sheet’s EU Accelerated Assessment Tracker.
### Requests Granted

**Status Of EU Accelerated Assessment Requests Granted Since January 2018**

<table>
<thead>
<tr>
<th>Applicant</th>
<th>INN &amp; brand name (where known)</th>
<th>Indication</th>
<th>Outcome of accelerated assessment request</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shionogi</td>
<td>cefiderocol</td>
<td>Treatment of infections caused by carbapenem-resistant gram-negative bacteria in adults with limited treatment options.</td>
<td>Accepted December 2018 CHMP meeting. Indication covered in a separate MAA. See following entry in table.</td>
</tr>
<tr>
<td>Shionogi</td>
<td>cefiderocol</td>
<td>Treatment of infections caused by aerobic gram-negative bacteria in adults with limited treatment options.</td>
<td>Accepted December 2018 CHMP meeting. No longer being reviewed under AA as of July 2019.</td>
</tr>
<tr>
<td>Karyopharm Therapeutics</td>
<td>selinexor</td>
<td>In combination with dexamethasone, for the treatment of patients with relapsed refractory multiple myeloma (RRMM) who have received at least three prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor (PI), one immunomodulatory agent (IMiD), and one anti-CD38 monoclonal antibody (mAb), and to their most recent treatment regimen (pan-transferrin refractory MM).</td>
<td>Accepted December 2018 CHMP meeting. No longer being reviewed under AA as of June 2019.</td>
</tr>
<tr>
<td>Stemline Therapeutics</td>
<td>tagraxofusp (SL-401/Elozonali)</td>
<td>Treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN).</td>
<td>Accepted November 2018 CHMP meeting. No longer being reviewed under AA as of July 2019.</td>
</tr>
<tr>
<td>Daiichi Sankyo Europe</td>
<td>quisartelib</td>
<td>Treatment of relapsed or refractory acute myeloid leukemia (AML) which is FLT3-ITD positive.</td>
<td>Accepted September 2018 CHMP meeting. No longer being reviewed under AA as of June 2019.</td>
</tr>
<tr>
<td>TheraBiologics/TaiMed Biologics</td>
<td>ibalizumab (Trogaran)</td>
<td>Treatment of multidrug-resistant HIV.</td>
<td>Accepted July 2018 CHMP meeting. No longer being reviewed under AA as of June 2019.</td>
</tr>
<tr>
<td>AveXis/Novartis</td>
<td>onasemnogene abpavovec (AVXS-101/Zolgensma)</td>
<td>Treatment of pediatric patients diagnosed with spinal muscular atrophy (SMA) Type 1.</td>
<td>Accepted July 2018 CHMP meeting. No longer being reviewed under AA as of July 2019.</td>
</tr>
<tr>
<td>Loxo Oncology/Bayer</td>
<td>larotrectinib</td>
<td>Treatment of adult and pediatric patients with locally advanced or metastatic solid tumors (excluding primary central nervous system tumors) with a neurotrophic tyrosine receptor kinase (NTRK) gene fusion after prior standard therapy or as initial therapy when there is no adequate treatment option.</td>
<td>Accepted July 2018 CHMP meeting. No longer being reviewed under AA as of December 2018.</td>
</tr>
</tbody>
</table>

**AA granted and MAA under review**

<table>
<thead>
<tr>
<th>Applicant</th>
<th>INN &amp; brand name</th>
<th>Indication</th>
<th>Outcome of accelerated assessment request</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ailylam</td>
<td>givosiran</td>
<td>Treatment of acute hepatic porphyria in adults and adolescents.</td>
<td>Accepted May 2019 CHMP meeting.</td>
</tr>
<tr>
<td>Astellas Pharma</td>
<td>blinatumomab (Xospata)</td>
<td>Treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation (FLT3mut+).</td>
<td>Accepted January 2019 CHMP meeting.</td>
</tr>
<tr>
<td>MSD</td>
<td>V920 (GVVSYAG-ZSEO-5P)</td>
<td>Active immunization of at-risk individuals 18 years and older in reactive use situations to protect against Ebola Virus Disease (EVD) caused by Zaire Ebola virus.</td>
<td>Accepted January 2019 CHMP meeting.</td>
</tr>
<tr>
<td>Roche</td>
<td>palatuzumab vedotin</td>
<td>Treatment of relapsed and refractory patients with diffuse large B-cell lymphoma.</td>
<td>Accepted December 2018 CHMP meeting.</td>
</tr>
</tbody>
</table>

*Ailylam announced on 1 July that it had filed for EU approval of givosiran. The product does not appear on the EMA’s list of products under review as of 9 July; these lists only include medicines whose applications have been validated at the time the lists are completed.*

**AA granted, MAA review completed under AA and approved as of 9 July 2019**

<table>
<thead>
<tr>
<th>Applicant</th>
<th>INN &amp; brand name</th>
<th>Indication</th>
<th>Outcome of accelerated assessment request</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shire Pharmaceuticals</td>
<td>lanadelumab (Takzyno)</td>
<td>Routine prevention of angioedema attacks and control of symptoms of hereditary angioedema (HAE) in patients aged 12 years and older.</td>
<td>Accepted February 2018 CHMP meeting. Approved 22 November 2018.</td>
</tr>
<tr>
<td>bluebird bio</td>
<td>Zynteglo (autologous CD34+ cells encoding (AA-187Q-globin gene)</td>
<td>For transfusion-dependent β-thalassemia (TDT) in patients with non-β(0)β(0) genotypes.</td>
<td>Accepted July 2018 CHMP meeting. Approved 29 May 2019.</td>
</tr>
</tbody>
</table>
Bluebird Seeks EU Fast-Track Review For Lenti-D Gene Therapy

Executive Summary
Bluebird bio is planning to file its EU marketing application for Lenti-D this year, before it files for approval in the US in mid-2021.

The European Medicines Agency is deciding this week whether to fast-track bluebird bio’s planned EU marketing application for Lenti-D, an investigational gene therapy for boys with the rare neurogenerative disease, cerebral adrenoleukodystrophy (CALD).

Bluebird’s request for an accelerated assessment is listed on the agenda of the latest monthly meeting of the EMA’s drug evaluation committee, the CHMP, which is taking place from 20-23 July. The CHMP is also considering an application to fast-track artesunate for treating severe or complicated malaria in adults and children.

In May, bluebird said it expected to submit its marketing authorization application (MAA) to the EMA for Lenti-D by the end of 2020. Requests for an accelerated assessment are required to be submitted at least two to three months before the MAA is submitted.

In the US, the company has pushed back its plan to file a marketing application with the Food and Drug Administration for Lenti-D to mid-2021, due to the impacts of the COVID-19 pandemic on its business.

Major Public Health Interest
The EMA reserves accelerated assessments for drugs it believes to be of major public health interest, particularly from the point of view of therapeutic innovation. The fast-track mechanism can cut the time it takes the agency to evaluate an MAA from up to 210 days to up to 150 days (not counting clock stops when applicants have to provide additional information).

If approved for CALD, Lenti-D would provide patients with an alternative to the only current treatment for the disease, allogeneic hematopoietic stem cell transplant (allo-HSCT). According to bluebird, allo-HSCT can be beneficial if performed early but can also potentially lead to complications that could be fatal.

Lenti-D was accepted on the EMA’s priority medicines (PRIME) scheme for getting drugs for unmet medical needs to patients faster in July 2018. Sponsors that secure a place on PRIME are offered enhanced scientific and regulatory support from the EMA to help optimize their development plans, and the likelihood of having their eventual MAA reviewed under the accelerated assessment procedure, though the latter is not a given.

In the US, the FDA has granted Lenti-D breakthrough therapy designation, which is similar to PRIME. The FDA has also awarded the gene therapy rare pediatric disease designation.

Lenti-D has been granted orphan drug status in both the EU and the US for adrenoleukodystrophy, the most severe form of which is CALD.

EMA’s Decision
As for the EMA’s decision on the latest applications for accelerated assessment, the outcomes of such requests are published in the minutes of the CHMP meeting at which the requests are decided on. It usually takes at least six weeks for CHMP meeting minutes to be published. Some companies choose to disclose the outcome in the interim, but most do not. Companies sometimes submit their MAA before the minutes are issued, at which point it usually becomes clear whether
or not they have been granted accelerated assessment.

Once it is known, the outcome of the latest requests will be added to the Pink Sheet's EU Accelerated Assessment Tracker. (Also see “EU Accelerated Assessment Tracker” - Pink Sheet, 2 Jul, 2020.)
ViiV’s Fostemsavir Loses EU Fast-Track Status
Potential New HIV Treatment Reverts To Standard Review

Executive Summary
Viiv Healthcare’s marketing application for fostemsavir started off being fast-tracked through the review process at the European Medicines Agency in January but is now being reviewed under standard timelines. The product is being developed for the treatment of adults with multidrug resistant HIV-1 infection.

The EU marketing authorization application (MAA) for fostemsavir, ViiV Healthcare’s potential first-in-class attachment inhibitor for the treatment of HIV-1 infection, has lost its accelerated assessment status and is now being reviewed under standard review timelines at the European Medicines Agency.

Fostemsavir, for the treatment of HIV in adults with few treatment options available, first appeared on the EMA’s list of MAAs under evaluation by the agency’s Committee for Medicinal Products for Human Use (CHMP) in January 2020. (Also see “ViiV Wins Fast-Track Review At EMA For HIV Therapy” - Pink Sheet, 20 Jan, 2020.) In the EMA’s latest list, compiled on 8 June, the MAA is identified as no longer being reviewed under accelerated assessment.

The GlaxoSmithKline PLC company told the Pink Sheet that it was “asked by CHMP to take a longer clock stop to respond to questions” and that, as a result, “we were not able to stay on the accelerated timetable.”

Fostemsavir is under review at the EMA for use in combination with other antiretrovirals for the treatment of adults with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen due to resistance, intolerance or safety considerations. The drug is also under review in the US, a new drug application having been made in December 2019. (Also see “Keeping Track: US FDA’s Rejection Of First RMAT BLA Blemishes Otherwise Positive Week Of Non-Oncology News” - Pink Sheet, 9 Dec, 2019.) The product appears to have priority review in the US; this is similar to accelerated assessment in the EU. Viiv said the US prescription drug user fee date for a regulatory decision was 4 August, adding that it was possible that the Food and Drug Administration would act earlier under its procedures for expedited review.

It is not easy to persuade the EMA to grant an MAA accelerated assessment. Nor is it uncommon for an MAA to lose this status mid-review. According to the agency’s annual report for 2019, just three medicines were recommended for marketing authorization following an accelerated assessment. These were: Ervebo, the first ever Ebola vaccine, from Merck Sharp & Dohme; Astellas Pharma’s acute myeloid leukemia treatment, Xospata (gilteritinib); and Zynteglo, bluebird bio Inc.’s gene therapy for beta-thalassemia.

Accelerated Assessment
The accelerated assessment mechanism can cut the time it takes the EMA to evaluate an MAA from up to 210 days to up to 150 days (not counting clock stops when applicants have to provide additional information). The EMA reserves the measure for products it determines to be of major interest for public health and therapeutic innovation.

The change in status of the fostemsavir MAA will be reflected the Pink Sheet’s EU Accelerated Assessment Tracker in due course.
EMA Clarifies Fast-Track Mechanisms For COVID-19 Medicines & Vaccines

Executive Summary
From speeding up PIP agreements to starting rolling reviews, the European Medicines Agency has explained how it is accelerating its regulatory procedures for COVID-19 treatments and vaccines.

The European Medicines Agency has issued a detailed explanation of the rapid regulatory procedures it is making available to fast-track the development and approval of treatments and vaccines for COVID-19, and how developers can best use them.

The procedures, which include speeding up agreements for pediatric investigation plans (PIPs), rolling reviews of marketing applications and the EMA’s priority medicines (PRIME) scheme, are discussed in the EMA’s newly published “inventory” of fast-track tools for COVID-19.

“The rapid procedures described in the inventory can accelerate every step of a medicine’s regulatory pathway,” the EMA says, adding that it is “fully mobilized to deliver these fast-track assessments in the shortest possible timeframes while ensuring robust scientific opinions are reached.” They apply to new products as well as already authorized products that are being repurposed for COVID-19.

R&D
The inventory document says that for products under development, in the early stages and/or before they are submitted in a marketing authorization application (MAA), the agency has established:

• Rapid scientific advice, through which developers can receive guidance and direction on the best methods and study designs to generate robust data on their product, and on the manufacturing and control process to establish its quality. In the context of COVID-19, fees for scientific advice are waived and the procedure is reduced to a maximum of 20 days, compared with the usual 40-70 days. (Also see “COVID-19: EMA Makes Scientific Advice Free & Fast For Drug, Vaccine Developers” - Pink Sheet, 13 Mar, 2020.)

• Rapid agreement of PIPs and rapid compliance check. The total review time for a PIP for COVID-19 products will be reduced to 20 days, compared with up to 120 days of normal active review time. Where needed, the EMA also carries out a check to ensure companies comply with the agreed measures listed in each PIP before a marketing authorization can be submitted, which will now also be reduced, to four days.

The agency stresses that all these accelerated mechanisms will require developers to submit well-prepared dossiers to EMA. Developers of COVID-19 vaccines or therapeutics “should make contact as soon as possible, to discuss their strategy for evidence-generation, by emailing 2019-ncov@ema.europa.eu,” it says.

Evaluating Marketing Applications
Regarding the evaluation of MAAs, which usually involves a standard timeline of a maximum of 210 active days, the inventory explains how developers of COVID-19 products might be able to use the following procedures:

• Rolling review, an ad hoc mechanism used in an emergency context and which the EMA
recently started using for Gilead Sciences’ antiviral remdesivir for treating coronavirus infection. (Also see “EMA Begins Rolling Review Of Remdesivir For COVID-19” - Pink Sheet, 1 May, 2020.) Unlike under normal circumstances where all data supporting a MAA must be submitted at the start of the evaluation procedure, the rolling review procedure allows the EMA to assess data for a promising medicine as they become available. In the case of a rolling review, rapporteurs from the EMA’s drug evaluation committees, CHMP, are appointed while development is still ongoing. Several rolling review cycles can be carried out during the evaluation of one product as data continue to emerge, with each cycle requiring around two weeks, depending on the amount of data to be assessed, the EMA explains. Once the data package is considered complete, a developer submits a formal MAA to the EMA which is then processed under a shortened timetable. The duration of the procedure will depend on the amount of data not yet assessed as part of the rolling review cycles.

- Accelerated assessment, which can reduce the review time for products of major public health interest from 210 days to less than 150 days. In practice, where there is an urgent public health need, assessment timelines will be reduced to the absolute minimum, the agency says.

Also in the marketing authorization phase, the EMA says it is ready to apply further flexibility where it is established that shortening any other procedural step could have an important public health impact in dealing with the COVID-19 pandemic.

**Extending Indications**
The agency says that its various rapid procedures are also available for extensions of indications of already approved medicines that are being repurposed in the fight against COVID-19. Marketing authorization holders “are encouraged to share early information about their planned development for COVID-19 with the EMA (the appointed Product Lead) and the Rapporteurs,” it says.

**Compassionate Use, PRIME & Orphan Designation**
The inventory also describes the support the EMA can provide in the context of compassionate use programs. Such programs are set up by individual EU member states to give patients access to treatments that are still under development and have not yet been approved. The EMA says it can provide scientific recommendations as to how these medicines should be used in this context, to support a harmonized EU-wide approach. (Also see “EMA Issues Guidance On Compassionate Use Of Remdesivir For COVID-19” - Pink Sheet, 6 Apr, 2020.)

The agency adds that developers should also consider applying for a place on its PRIME scheme, which is designed to get medicines for unmet medical needs to patients faster. Developers accepted on PRIME are offered enhanced support from the EMA for the development of their product. This support is expected to help developers optimize their evidence generation, which should also facilitate accelerated assessment when their MAA is filed. In the context of COVID-19, PRIME is predominantly suitable for treatments and vaccines in earlier stages of development.

The EMA’s inventory document also notes that applications for orphan designation for the treatment or prevention of COVID-19 are not expected because of the high number of cases of infections in the EU and worldwide. Therefore, no specific consideration is provided in the document regarding rapid reviews of orphan designations. Developers should contact the Orphan Medicines Office in case they wish to discuss specific proposals, the agency says.
A detailed description of rapid procedures for further post-authorization activities will be considered once the first COVID-19 treatments or vaccines have been authorized.
Alexion Win Thwarts Roche’s EU Fast-Track Hopes

Executive Summary
Roche hopes that its investigational drug satralizumab for neuromyelitis optica spectrum disorder will win EU approval in the second half of 2020.

Roche has lost the fast track status it won for the EU marketing application it filed with the European Medicines Agency last October for satralizumab, the drug it is developing to treat the rare disease neuromyelitis optica spectrum disorder (NMOSD).

The EMA decided that the marketing authorization application (MAA) no longer merited accelerated assessment because a rival product had received pan-EU approval for NMOSD, Roche told the Pink Sheet. Alexion Pharmaceuticals’ Soliris (eculizumab) was approved in the EU for treating the disorder last August; Soliris also became the first treatment for NMOSD to win US approval last June.

Satralizumab has now reverted to the standard review timeline at the EMA, which is 210 days compared with 150 days for accelerated assessment (not counting clock stops in both cases when applicants have to provide additional information).

Roche believes its product could be approved in the second half of 2020. It said it was “very confident in the potential of satralizumab for NMOSD,” after two studies of the drug “met their primary endpoints, and importantly, demonstrated a well-tolerated safety profile with robust efficacy sustained for 144 weeks in a broad population of patients.”

The EMA reserves accelerated assessment for drugs it believes to be of major public health interest, particularly from the point of view of therapeutic innovation.

The agency granted the planned MAA for satralizumab accelerated assessment last July, around three months before Roche applied for approval. The EMA decision was based on “there not being any approved treatments for NMOSD in Europe,” the company said. (Also see “Rivals Await CHMP Decisions On Drugs For NMOSD” - Pink Sheet, 23 Jul, 2019.)

Roche continued: “There has since been an approval in Europe, which is a significant step forward for patients that we welcome. As a result, the EMA has reverted our application for satralizumab to standard review.”

The switch was disclosed by the EMA in its January 2020 list of MAAs under review.

Regarding Soliris’s EU authorization last year, the European Commission approved an extension of the existing marketing authorization of the product to include the treatment of NMOSD in adult patients who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of the disease.

Competitive Landscape
Roche and Alexion are among several companies targeting NMOSD, a lifelong and debilitating autoimmune disease of the central nervous system that damages the optic nerve and spinal cord, causing blindness, muscle weakness and paralysis.

Roche, which is developing satralizumab in collaboration with Chugai Pharmaceutical, presented Phase III results for the drug last September. While its SAkuraStar study failed to
beat the efficacy results achieved by Soliris in Alexion’s pivotal trial, the data was well-received, especially given the larger NMOSD population eligible for therapy (the Roche trials enrolled patients who were both seronegative and seropositive for AQP-IgG antibodies) and an easier administration schedule. Satralizumab is given once every four weeks by subcutaneous injection, while Soliris requires infusions every two weeks. (Also see “Roche Mounts NMOSD Challenge To Alexion’s Soliris” - Scrip, 12 Sep, 2019.)

In the US, the Food and Drug Administration granted satralizumab breakthrough therapy designation for treating NMOSD in December 2018 and is reviewing the product under a standard review. The FDA has indicated a target approval date of 15 August.

Satralizumab has been granted priority review in Canada and Switzerland and is designated as an orphan drug in the US, Europe and Japan. “We do not comment on the order of approvals, but are working closely with regulatory bodies across the globe to bring satralizumab to people with NMOSD as soon as possible,” Roche said.

Another company eyeing the NMOSD space is Viela Bio, a spin out from AstraZeneca’s biologics R&D arm, MedImmune. Viela is developing a drug called inebilizumab. In August 2019, the US FDA accepted the company’s biologics license application for the product for review. The FDA set a Prescription Drug User Fee Act date of 11 June.

Alexion is also lining up its next-generation follow-up to Soliris, Ultomiris (ravulizumab), for a license in NMOSD.

The change in status of the Roche MAA has been reflected in the Pink Sheet’s EU Accelerated Assessment Tracker. (Also see “EU Accelerated Assessment Tracker” - Pink Sheet, 21 Feb, 2020.)

Sign up to a Pink Sheet trial to access more recent coverage on accelerated approvals