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# A Candid Behind-The-Scenes Look At PRIME with Novimmune & Biogen

by Neena Brizmohun

Novimmune and Biogen encountered surprises, challenges and opportunities with PRIME, the European Medicines Agency's new priority medicines scheme. The two companies have some advice on how to keep pace with expectations under the initiative and make the most of the scheme for taking drugs for unmet medical needs to patients faster.

Novimmune met the invitation earlier this year to attend a kick-off meeting with the European Medicines Agency under the regulator's new priority medicines (PRIME) scheme with some trepidation.

"It came as a surprise to us that we got to see the EMA so quickly," Novimmune's Chief Medical Officer, Cristina de Min, said. It had not been long since the company had learnt that its investigational drug for treating hemophagocytic lymphohistiocytosis (HLH) in children had been among the first wave of products to get accepted on the much talked about scheme, which is designed to speed patient access to drugs for unmet medical needs. Moreover, the EMA had asked to see Novimmune just two days before the Swiss company was due to attend a previously arranged meeting with the US Food and Drug Administration.

"We were not ready and we tried to negotiate [with the EMA]," de Min explained. But in the end, the company attended the kick-off meeting as requested. "I'm glad we did."

Kick-off meetings under PRIME involve a company meeting with an EMA rapporteur that has been assigned to it under the scheme and a multidisciplinary group of experts from relevant EMA scientific committees and working parties. The purpose of the meeting is to discuss potential issues relating to a drug's development contained in a briefing document that the company would have previously submitted to the agency. The regulator also provides preliminary guidance on the overall plan and develops a schedule for giving regulatory and scientific advice and for the submissions of applications to fulfil legislative requirements (e.g., the paediatric

investigation plan).

The kick-off meeting was "really important to us in appreciating the challenges and also the opportunities" involved with developing NI-0501, Novimmune's drug for treating primary HLH, de Min said. In fact, she continued, "I was more surprised by the opportunities than the challenges".

According to de Min, PRIME has given Novimmune a better appreciation of the development risks involved with targeting a life-threatening syndrome like HLH, which is rare, occurs mainly in pediatrics, can be difficult to diagnose and for which very little published prospective data exists.

Companies considering applying for PRIME will need to be very good at planning, de Min warned. They need to be prepared to keep pace with the work that will be expected of them in terms of providing the EMA with punctual development updates on their plans as more evidence becomes available. They should also expect to change how they work internally and involve more functions within their organization much earlier on in their development plan than usual if they want to make the most of the scheme.

PRIME requires a lot of discipline for companies internally, de Min said. "It's a challenge and an opportunity at the same time."

de Min was speaking at the Annual European Medicines Agency Review of the Year and Outlook for 2017 conference in London on Dec. 2. The conference was co-hosted by the EMA and TOPRA, The Organisation for Professionals in Regulatory Affairs.

## Biogen And Thinking Ahead About Post-Authorization Plans

Biogen was also among the first companies to receive PRIME designation. It reports a similarly expeditious and positive experience of its kick-off meeting for aducanumab, the company's investigational treatment for early Alzheimer's disease.

The EMA is open to schedule the first meetings very quickly, said Simon Bennett, the company's Director of Regulatory Policy EU, who was also speaking at the EMA's annual conference.

"It was clear from before the meeting that the rapporteur had looked very carefully" at the briefing package on aducanumab that Biogen had sent the agency beforehand, Bennett commented, adding that the company received "very constructive feedback and comments during the meeting."

Companies applying for PRIME should not underestimate the need to discuss how they will collect post-market data at the start of their program.

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Even though aducanumab is at an early development stage, discussions at the kick-off meeting covered issues such as post-authorization planning - which Bennett said were key for Biogen's particular product - and the need to engage with health technology assessment (HTA) bodies and patient advocacy groups. "The challenges that we envisage with the Alzheimer's program is around last-stage, post-marketing data collection… and continuing in monitoring the efficacy of the product once its licensed," he said.

PRIME was launched in March and 14 companies have so far received a designation under the scheme. Designees receive enhanced support from the EMA to help optimize their product development and the potential for an accelerated review.

## Involving Disciplines Across A Company is Key

Both speakers stressed the need for companies to bear in mind that they will have to involve more of their internal functions than normal early in development if they want to take part in PRIME.

PRIME requires a cross-functional involvement within an organization and input from people from different disciplines, de Min said. This is not usually the case when companies attend a typical regulatory meeting, she explained, adding that for an SME, like Novimmune, it was imperative to work out how to manage human and financial resources early on.

Biogen also found it had to involve "many more functions internally" for its kick-off meeting. "This was something that was different within Biogen," Bennett said, reflecting on how the company approached normal EMA meetings. A multidisciplinary approach is necessary as all aspects of a development program are key to the potential success of an accelerated process, he noted.

Biogen had prepared its application for PRIME even before the scheme was formally launched and had put together its briefing package on aducanumab in line with the EMA's now adopted guideline on the initiative (*Enhanced early dialogue to facilitate accelerated assessment of PRIority MEdicines (PRIME)*).

An important part of the company's briefing package was the inclusion of "a table of potential issues that we wanted to address and which stakeholder we wanted to be involved," Bennett said. That table now serves as a "living document" that will continue to be revised as the company proceeds through PRIME.

As for some of the early tools that PRIME offers, Bennett said that the EMA rapporteur and the dedicated contact at the agency, who are assigned to companies early on in the scheme, were "really valuable."

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Rapporteurs are normally assigned just prior to a marketing authorization application (MAA) being filed. The advantage of having them assigned early, Bennett explained, was that they could identify potential issues or concerns in development that can be mitigated early. They become more familiar with the product and strategy and provide guidance throughout development and the eventual MAA assessment. Hopefully, all this will lead to fewer questions when the file gets submitted, Bennett said.

The advantages for Biogen of being assigned a dedicated contact at the agency were that "many conversations" took place between the two on "what to expect for the kick-off meeting and how best to prepare."

For example, Biogen had to prepare a slide deck structured according to an agenda it received from the EMA a week before the meeting. The slides were designed to address points the rapporteur had raised from its review of the briefing package. "The agenda really did drive the meeting," Bennett said.

"The kick-off meeting was a very collaborative process between the company and the EMA," he said. Biogen learnt that for PRIME to work effectively, the company should seek, as far as possible, centralized scientific advice rather than national scientific advice.

The EMA also proposed using a shorter lead-in time to centralized advice (40 days rather than 70 days), which "in a 5-6-month procedure… is an advantage," Bennett said. Following post-meeting discussions with the EMA, however, Biogen was told that if it was contemplating parallel scientific advice from the agency and HTA bodies, it should consider using the full 70-day procedure due to the complexity of discussions and allowing HTA bodies to become completely familiar with the data and strategy.

## Not Many Improvements… Except…

Commenting on whether the PRIME procedure could be improved, Bennett said the only thing Biogen found tricky was in finding the right balance between producing a short and focused package (as per the guidance) while at the same time still covering all the topics listed in the annex of the guidance in sufficient detail. Otherwise, the guidance on the application and kick-off meeting are "clear and relatively straightforward to follow, "he said.

Bennett also pointed out that potential applicants should understand that while national scientific advice can continue to be sought, this may not always be possible and can be dependent upon the rapporteur assigned.

## Time To Market

Regarding how much earlier PRIME might enable Biogen to take aducanumab to market, it is still too early to tell. "If things go well and if the product goes through accelerated assessment,

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obviously we will save time there," Bennett said.

But the point is not so much about the time to market or time to approval, but more about patients getting access to the drug once it is approved, Bennett commented, adding that including HTA bodies, payers and patient groups in discussions with the regulators was a critical component of PRIME.

That said, he believes that being in the scheme will make it possible for aducanumab to become accessible as quickly as possible.

The expectation is that the additional scientific and regulatory support provided under PRIME will give a better structure to the overall development plan and to the regulatory opinion in terms of the post-authorization work and in terms making the whole package look better to downstream stakeholders.

The importance of engaging HTA bodies has already been recognized by the EMA. "We are actively discussing with them about how we can really complement each other," said the head of the agency's Scientific & Regulatory Management department, Jordi Llinares Garcia, who was also speaking at the conference in London.

As for Novimmune, de Min said the kick-off meeting entailed "a comprehensive and multidisciplinary discussion" that helped define the "prioritization of critical topics requiring scientific advice." She noted that a Phase II/III study was already ongoing at the time of the PRIME designation but that very few patients were involved.

de Min also believes that the "continuity and proactivity" offered under PRIME throughout the lifecycle of the company's molecule, gives Novimmune the opportunity to review the "full cycle" of the product. She explained that while NI-

### *Quick Facts About PRIME*

The European Medicines Agency's priority medicines (PRIME) scheme was launched on March 7, 2016 to enhance support for the development of medicines that target an unmet medical need.

Under the scheme, the EMA offers early and proactive support to medicine developers to optimize the generation of robust data on a medicine's benefits and risks and enable accelerated assessment of medicines applications. The aim is to speed up the evaluation of medicines so that they can reach patients earlier.

PRIME is open to all companies on the basis of preliminary clinical evidence, though SMEs and applicants from the academic sector can apply earlier on the basis of compelling non-clinical data and tolerability data from initial

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0501 is initially being developed for the second-line treatment of primary HLH, the company also plans to investigate use of the product in first-line treatment and other forms of HLH.

The ability to negotiate "what is feasible" during the kick-off meeting was also "very much appreciated," de Min said. By discussing how a company should structure its regulatory submission forces us to think about the future and what's important, she said.

*From the editors of Scrip Regulatory Affairs.*

clinical trials.

The scheme has a tough entry criteria and applicants must provide early clinical data to show that their product has the potential to significantly address an unmet clinical need.

As of Sept 21, 2016, 14 products had received a PRIME designation and 46 applications had been rejected.