Evaluate Vantage

June 26, 2017

Roche brings new blood to haemophilia A

Madeleine Armstrong

Watch out Shire – Roche is coming for you in haemophilia A. Impressive data from the Haven 1 study of its bispecific antibody emicizumab should do nothing to change *EvaluatePharma* sellside consensus, which suggests that Roche's project will almost catch Shire's market leader Advate by 2022 (see table below).

However, the more detailed Haven 1 results released today highlighted a divide between responders and non-responders to emicizumab, with the latter group making up around a third of patients. This, along with lingering safety concerns with emicizumab, will give Shire confidence that it can remain dominant.

Top-five haemophilia A products in 2022

			WW sales ($m)			
Product	**Company**	**Status**	**2016**	**2018e**	**2020e**	**2022e**
Advate	Shire	Marketed	1,279	2,065	1,945	1,755
Emicizumab	Roche	Phase III	-	174	876	1,636
Afstyla	CSL	Marketed	147	461	730	1,000
Kogenate	Bayer	Marketed	1,290	1,142	1,019	852
NovoSeven	Novo Nordisk	Marketed	1,168	1,049	811	691

Source: EvaluatePharma.

The headline result of Haven 1, which enrolled patients who had developed antibodies rendering front-line factor VIII clotting factors ineffective, was an 87% reduction in bleed rate with prophylactic emicizumab treatment. This was significantly better than the control group, which received on-demand bypassing agents, with a p value of 0.0001.

Perhaps more importantly, 63% of patients in the treatment group reported zero bleeds compared with 6% in the control arm. Full data will be reported at the International Society on Thrombosis and Haemostasis (ISTH) meeting in Berlin on July 10.

Roche will also present interim results from the first 19 patients enrolled in Haven 2, a study in patients aged under 12. The company said that at 12 weeks only one patient receiving emicizumab reported a treated bleed, and that there were no reported joint or muscle bleeds.

Responders vs non-responders

Investors will no doubt be interested in Roche's explanation for the stark difference between the two thirds of patients that responded to emicizumab in Haven 1 and the remaining third that did not. The former group experienced zero bleeds while the latter had an annual bleed rate (ABR) of 7.8, noted Bernstein analysts, who cited an ABR of less than 5 as ideal.

But they added that "high efficacy in a subgroup is better than mixed results in all patients", saying this would allow quicker penetration into that population. The analysts speculated that an assay could be developed to identify responders – something that payers might require to prevent treatment of non-responders, a potential barrier to emicizumab's market entry.

The Bernstein analysts also wrote that current non-responders might just need a higher dose; however, this could exacerbate existing safety worries: as previously reported there were two thromboembolic events and three cases of thrombotic microangiopathy in Haven 1. One of these patients died but this was deemed unrelated to treatment (*The risks keep rising for Roche's haemophilia hope, February 23, 2017*).

Roche blamed “repeated high doses of a bypassing agent” for the thrombotic events, but some believe that the combination of emicizumab and bypassing agents – specifically, Shire’s Feiba – could be causing the problem.

Leerink analysts have speculated that Roche might need to carry out further pre-registration studies to investigate this, which could delay its entry to market. At the very least, more trials of the combination seem likely to be a post-approval requirement.

Roche plans to file for approval this year, and initially plans to seek the go-ahead in patients who have developed inhibitors – the aforementioned factor VIII antibodies – where emicizumab has breakthrough therapy designation. Options for these patients are very limited, which will help Roche’s cause, but the company might face more scrutiny over safety if it wants to expand emicizumab’s use into the broader haemophilia A market.

The Haven 3 study, in patients without inhibitors, is due to complete next year. If Roche can show, as hoped, that emicizumab does not cause the development of inhibitors, this would give it an edge. And its once-weekly subcutaneous delivery should be a plus in a market dominated by infused factor VIII agents – Roche is also trialling less frequent dosing.

However, all this will be for nothing if safety trips up emicizumab at the final hurdle.

Trial	**ID**
Haven 1	NCT02622321
Haven 2	NCT02795767
Haven 3	NCT02847637

To contact the writer of this story email Madeleine Armstrong in London at madeleinea@epvantage.com or follow @ByMadeleineA on Twitter