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Ash 2022 – Argenx faces Vyvgart questions

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As the group looks to expand into immune thrombocytopenia, there are several reasons to be cautious.

Immune thrombocytopenia is a disease for which patients could do with more options. Argenx hopes to add to these with Vyvgart, which has bagged a prestigious press slot at this year's Ash meeting.

However, there are outstanding questions about the drug here, including whether a marginal win in the Advance IV study, being presented during a plenary session tomorrow, will be enough to support approval. And, even if Vyvgart gets to market, it is unclear how it might fit into the treatment landscape: Argenx's study enrolled a heavily pretreated population, and oral contenders could be coming.

Argenx is developing intravenous and subcutaneous versions of Vyvgart, and hopes to have both available for all indications currently in development. In ITP, Advance IV tested the intravenous form, and Argenx is awaiting data from the subcutaneous Advance SC trial, due in the second half of 2023, before filing a single package with the FDA.

A spokesperson for Argenx does not anticipate any problems with this approach, despite the fact that the group has previously said that the formulations are seen as different products by regulators.

"ITP is the only indication where the FDA stated two registrational trials would be necessary, so we are conducting the subcutaneous study as the second registrational study," the spokesperson told *Evaluate Vantage* under embargo before the meeting started.

Post-steroids?

ITP is an autoimmune disorder involving platelet destruction, which leads to excessive bruising and bleeding. The first-line treatment is usually corticosteroids, but most patients cannot tolerate these long-term and can relapse once steroids are tapered, Dr Cynthia Dunbar of National Heart Lung and Blood Institute said during a pre-Ash media briefing.

The next step is spleen removal or thrombopoietin receptor agonists like Novartis's Promacta or Amgen's Nplate. Another second/third-line option is Rituxan, although this has fallen out of favour lately owing to its long-term depletion of patients' antibodies, Dr Dunbar said.

As for how Vyvgart might fit in, it is notable that the Advance IV trial enrolled patients who had failed at least one prior therapy, and 67% of patients had received three or more prior therapies.

At a press conference today, Dr Catherine Broome of Georgetown University, Washington, DC said Vyvgart could be a “great drug for patients who’ve not responded to a steroid or thrombopoietin receptor agonist”. She estimates that up to 30% of ITP patients fail multiple lines of therapy.

“Whether it will be able to show significant efficacy in a not so heavily pre-treated population remains to be seen,” she told *Evaluate Vantage* in a later interview, but added: “The way the drug works, there shouldn't be a reason why it wouldn't be equally effective in earlier lines of therapy.”

Stifel analysts reckon that Vyvgart could bring in sales of over $1bn in ITP, based on the 70% or so patients who relapse after steroids.

ITP Advance

In Advance, patients received IV Vyvgart weekly or every other week, or placebo, for 24 weeks. As previously detailed in the Ash abstract, 22% of those receiving Vyvgart achieved a sustained platelet response, the primary endpoint, versus 5% of the placebo group (*Ash 2022 preview – Argenx’s expansion plans come into focus, November 10, 2022*).

A platelet response was defined as having platelet counts greater than or equal to $50x10^9$/l on at least four of the last six scheduled visits between weeks 19 and 24 of treatment.

The result was statistically significant, with a p value of 0.0316. Stifel has questioned whether this marginal result will support approval, although a bigger issue is probably what this close win might mean for the upcoming Advance SC study of the subcutaneous formulation.

This concern appears to have been behind Argenx’s move to increase enrolment in that study, which delayed its readout. It had originally been expected in the first quarter.

Another potential issue is that, in Advance IV, Vyvgart did not lead to a significant decrease in bleeding events. However, Argenx’s chief medical officer, Luc Truyen, told *Vantage* ahead of Ash: “We had relatively low bleeding events at baseline so it was difficult to create a statistically significant delta.” He noted a numerical decrease in bleeds with Vyvgart versus placebo.

Dr Dunbar agreed that this finding was not a cause for concern, stressing that Advance was a relatively short study.

In general, Argenx is well ahead of its anti-FcRn rivals. However, the ITP space could soon be evolving and another anti-FcRn player, UCB, recently dropped out of the disease, citing increasing competition. Oral projects pose a particular threat, and one in development is Sanofi’s BTK inhibitor rilzabruitnib; however, this has already failed in pemphigus so is far from a dead cert.

Targeting FcRn: clinical-stage projects		
Project	**Company**	**Note**
Approved		
Vyvgart (efgartigimod)	Argenx	gMG: IV version approved, SC version has Pdufa Mar 20, 2023; ITP: ph3 IV Advance IV data at Ash 2022, Advance SC data due H2 2023; CIDP Adhere due Q1 2023; Pemphigus Address due H2 2023
Phase 3		
Rozanolixizumab	UCB	SC infusion; Mycaring in gMG reported May 2022; development in ITP deprioritised
Nipocalimab	J&J (via Momenta)	IV; ph3 in gMG; ph2/3 in wAIHA & CIDP
Batoclimab (IMVT-1401)	Immunovant	SC; ph3 in gMG & TED; previously linked with cholesterol increases in ph2 Ascend-Go2
CIDP=chronic inflammatory demyelinating polyneuropathy; gMG=generalised myasthenia gravis; ITP=immune thrombocytopenia; TED=thyroid eye disease; wAIHA=warm autoimmune haemolytic anaemia. Source: Evaluate Pharma & clinicaltrials.gov.		

This story has been updated following an interview with Dr Catherin Broome.

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