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Horizon looks for a new growth driver

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The company plans to make the most of its head start with the Graves' disease project teprotumumab, which is forecast to become its biggest product.

Companies that count their chickens before they are hatched can end up with egg on their faces. But Horizon Therapeutics' optimism over its thyroid eye disease project, teprotumumab, got another boost earlier this month with more impressive data from the pivotal Optic study.

The asset looks odds-on to get the nod by its PDUFA date of March 8, although there are still questions over reimbursement and whether it will get the go-ahead in mild as well as more severely affected patients. Horizon plans to commercialise teprotumumab itself, and it is clear to see why – the drug is forecast to be the group's best seller by 2024, according to *EvalautePharma* consensus.

The company is trying to transform from a speciality pharma group to an orphan disease and rheumatology player, and teprotumumab is a key part of that strategy.

Horizon Therapeutics' top sellers in 2024			
		Annual sales ($m)	
Product	**Indication**	**2018**	**2024e**
Teprotumumab/ HZN-001	Thyroid eye disease	-	484
Krystexxa	Gout	259	474
Ravicti	Urea cycle disorders	227	335
Procysbi	Nephropathic cystinosis	155	226
Pennsaid 2%	Osteoarthritis pain	190	143
Actimmune	Chronic granulomatous disease	106	95
Vimovo	Osteoarthritis/rheumatoid arthritis pain	68	44
Rayos	Rheumatoid arthritis/polymyalgia rheumatica	61	42
Duexis	Osteoarthritis/rheumatoid arthritis pain	115	41
Buphenyl	Urea cycle disorders	22	16
All marketed apart from teprotumumab. Source: EvaluatePharma.			

Horizon should benefit from the fact that there are no FDA-approved therapies for thyroid eye disease, an autoimmune condition that leads to eye bulging and sometimes blindness. The disease can occur on its own but is also present in up to half of people with Graves' disease, which causes an overactive thyroid.

Currently, patients are managed using steroids and radiotherapy; orbital decompression surgery is sometimes carried out, although this comes with its own risks, and Stifel analysts have described the procedure as "terrible" for patients and something that eye surgeons are keen to avoid. Roche's anti-CD20 antibody Rituxan is also used off-label, but is reserved for severe cases, "with limited effect on disease progression" according to Stifel.

There are other candidates in development for Graves', but teprotumumab, also known as HZN-001, is by far the most advanced. This could prove an obstacle to the other hopefuls, according to Elizabeth Thompson, Horizon's vice-president of rare disease clinical development.

She pointed to the potential challenge of running placebo-controlled trials with these agents should teprotumumab get approved, saying that using teprotumumab as an active comparator might become the only way forward. "There's now an established efficacy bar that any new agent would need to meet," Ms Thompson told *Vantage*.

Novartis, for one, is not currently pursuing its anti-CD40 MAb iscalimab in Graves', despite clearing phase II, a spokesperson for that company told *Vantage*, although he added that this might change. For now, the Swiss group is focused on other indications including kidney and liver transplantation, Sjögren's syndrome, systemic lupus erythematosus and lupus nephritis.

Selected projects in development for Graves' disease				
Project	**Company**	**Description**	**Trial(s)**	**Primary completion**
Filed				
Teprotumumab/ HZN-001	Horizon Therapeutics	Anti-IGF-1R antibody	Optic, NCT03298867	Met all primary and ranked secondary endpoints
Phase II				
IMVT-1401/RVT-1401	Roivant/Immunovant	Anti-FcRn antibody	NCT03922321; NCT03938545	Dec 2019; Jan 2021
CFZ533/iscalimab*	Novartis/Xoma	Anti-CD40 antibody	NCT02713256	Apr 2017
Phase I				
K1-70	AV7	TSH receptor antagonist	NCT02904330	Feb 2020
ATX-GD-59	Apitope International	TSH-receptor-derived apitopes	NCT02973802	Feb 2018
Source: EvaluatePharma, clinicaltrials.gov.				

The bar for companies hoping to catch up with teprotumumab in Graves' now looks pretty high. Horizon reported in February that the Optic study had met its primary endpoint, with 83% of teprotumumab-treated patients seeing a reduction of 2mm or more in proptosis – eye bulging – at six months, versus 10% on placebo (*Horizon eyes 2020 approval for Grave's orbitopathy, March 1, 2019*).

New data presented at the American Society of Ophthalmic Plastic and Reconstructive Surgery meeting in October, on secondary endpoints including double vision and quality of life, have strengthened Horizon's cause. Stifel analysts quoted one attendee, who described teprotumumab as "the brightest thing to happen in thyroid eye disease in my entire career".

However, it might not all be plain sailing for the company. It is unclear whether the FDA will give teprotumumab the green light in mild disease; Optic only enrolled moderate-to-severe patients. Ms Thompson refused to be drawn on this, saying it was up to the agency. As for potential off-label use in mild patients in the event of a narrow approval, she said that physicians would have to make their own decisions here.

Reimbursement could also be an issue: teprotumumab will not immediately have a permanent J-code, which is used for Medicare billing, and might not receive one until early 2021. A spokesperson for Horizon told *Vantage* that this would not affect the launch; if approved, the company plans to initially commercialise the project using a miscellaneous J-code, which she described as common practice.

Horizon has the resources to launch teprotumumab itself. The company had $866m in cash at the last count and already has a 50-person sales force in place, according to Stifel, although the spokesperson would not confirm this number.

The group's continued transformation depends on it making a success of teprotumumab. Horizon will have to hope that the unmet need will help the project get a broad label and spur strong uptake.

This story has been updated to clarify the difference between thyroid eye disease and Graves'.

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