Evaluate Vantage

April 19, 2023

Viridian aims to prove itself in thyroid eye

Elizabeth Cairns

Forthcoming data will see the group take on Horizon, but subcutaneous projects could pose the real threat.

Horizon Therapeutics' Tepezza is the only drug approved for thyroid eye disease, and last week its reach increased. In the wake of data suggesting Tepezza works in patients with chronic but mild disease, the FDA approved a change to the drug's label, specifically stating that it can be used "regardless of thyroid eye disease activity or duration".

Whether payers will expand reimbursement to match is another question, though with Amgen's takeover of Horizon in the works powerful marketing muscle could soon be brought to bear. What is not in question, however, is that a competitor is hard on Horizon's heels. Viridian Therapeutics will shortly report mid-stage data on VRDN-001 in both chronic TED, and success could begin to change the landscape.

Company	Viridian Therapeutics
Product	VRDN-001
Market cap	$1.2bn
Product NPV	$2.0bn
% of market cap	167%
Event type	Phase 1/2 results
Date	Q2 2023

Data from two trials of VRDN-001, which like Tepezza is an IGF-1R blocker, ought to emerge in the next couple of months. The most commercially important will be the phase 3 readout in patients with severe active TED, due in early 2024.

The Thrive trial is more than twice the size of Tepezza's approval trial in the severe active population, Optic, but has similar enrolment criteria and the same primary endpoint – proptosis responder rate (PRR) after six months' treatment. Thus experts and investors alike will be looking for a result that matches or exceeds the 73% treatment effect seen in Optic.

Viridian has not released a great deal of data from its phase 1/2 study of VRDN-001 in this setting, but the results included in a company presentation show that 11 of 16 evaluable VRDN-001 recipients hit the 2mm improvement in proptosis that defined response, versus none of the five placebo subjects, after six weeks' treatment. With 21 patients in the treatment group this gives a placebo-adjusted PRR of 52% in the ITT population. The tiny patient numbers and different time point, however, make it hard to deduce what this might mean for the Thrive trial.

Ah, go on, TED

The more immediate big readout, which is coming this quarter, is from the phase 1/2 trial of VRDN-001 in subjects with mild, long-term TED – a similar group to that enrolled in the phase 4 trial in which Tepezza just succeeded. The study consists of two cohorts of eight patients each, who will receive either two doses of 3mg/kg or 10mg/kg every three weeks, as well as two patients given placebo.

Some analysts regard Horizon's phase 4 data as de-risking the readout. Despite the differences between Horizon's and Viridian's chronic studies – which include dosing, treatment duration and disease severity – SVB analysts believe that VRDN-001 could differentiate itself from Tepezza in the commercially important chronic, mild TED population.

Viridian's former chief executive Jonathan Violin has previously told *Vantage* that compared with Tepezza VRDN-001 might have "faster onset, earlier symptom relief, potentially higher efficacy, shorter course of treatment, all of which we think will come in a package with a very attractive safety profile."

The bar for Viridian in thyroid eye disease					
Project (company)	Tepezza (Horizon)		VRDN-001 (Viridian)		
Trial	Ph3 (Optic, NCT03298867)	Ph4 (NCT04583735)	Ph 1/2	Ph2/3 (Thrive, NCT05176639)	Ph1/2
Population	Moderate-to-severe active TED	Mild, chronic TED	Moderate-to-severe active TED	Moderate-to-severe active TED	Mild, chronic TED
N	83	62	21	184	18
CAS	≥ 4	≤ 1	≥ 4	≥ 4	≤ 7
Duration of disease	< 9mth	2-10yrs	< 1yr	< 1yr	> 1yr
Proptosis	n/a	≥ 3mm	n/a	n/a	≥ 3mm
Primary endpoint	PRR	Change in proptosis	Unknown	PRR	Unknown
Pbo-adj PRR in ITT pop	73% (p<0.001)	37% (p=0.0134)		Data expected Q2 2024	Data expected Q2 2023
Pbo-adj chg in proptosis in ITT pop	2.79mm	1.49mm (p=0.0004)			

*CAS=clinical activity score. PRR=proptosis responder rate; proptosis response defined as reduction of at least 2mm. All data at 24wk. *Vantage calculation. Source: NEJM, clinicaltrials.gov, company communications.*

Another chance for Viridian to distinguish itself is with a subcutaneous TED therapy. The group is working on a subcutaneous form of VRDN-001, but also on two other candidates, -002 and -003. Early clinical data on all three should arrive by the end of the year, and then Viridian will decide which to take forward. Horizon is developing a subcutaneous form of Tepezza, too.

Wells Fargo analysts believe the convenience of a subcutaneous offering could play a major role, particularly in chronic TED.

Sling Therapeutics and Acelyrin are the other groups known to be exploring IGF-1R inhibition in TED, and Sling's therapy, the only oral small molecule in the clinic with this mechanism, could prove a contender if its mid-stage study succeeds later this year.

Currently the sellside forecasts 2028 sales of $989m for VRDN-001, versus $4.2bn for Tepezza. By the summer, it will be clear whether Viridian might close that gap – though if the Amgen-Horizon deal goes through

Viridian will be up against a major competitor.

IGF-1R therapies for active and chronic TED			
Company	**Project**	**RoA**	**Status**
Horizon	Tepezza	IV	Approved in US since 2020; recent ph4 data could expand use into mild, chronic patients
	Tepezza SC	SC	Ph1 began Jul 2022
Viridian	VRDN-001	IV	Ph3 Thrive trial in moderate-to-severe active TED and Ph1/2 in mild, chronic TED could report Q2 2023
	VRDN-001 SC	SC	Ph1 planned; data expected 2023
	VRDN-002	SC	Ph2 data expected 2023
	VRDN-003	SC	Ph1 planned; data expected 2023
Sling Therapeutics	Linsitinib	Oral	Ph2b Lids trial in active, moderate-to-severe TED could report 2023
Acelyrin (formerly Valenzabio)	Lonigutamab (VB421)	SC	Ph1/2 trial in severe, active TED could report 2024
Source: Evaluate Pharma, clinicaltrials.gov, Viridian presentation.			

Note: text has been updated to correct time point of data from Viridian's phase 1/2 trial in moderate-to-severe active TED; data was also removed from the table.