Evaluate Vantage

May 24, 2018

Can Acceleron stem Celgene’s bleeding?

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Celegene's fortunes linked to partner Acceleron's success in key late-stage trials.

As Acceleron gears up to release the first pivotal data on its most advanced pipeline candidate, spare a thought for its beleaguered partner, Celgene, for which the stakes are also high. The novel anaemia treatment luspatercept is widely expected to deliver positive phase III data and anything less will be a big blow to both drug developers.

Two studies are due to report by mid-year, in myelodysplastic syndrome (MDS) and beta thalassemia; the former is particularly crucial as it is a larger indication. The partners want to show that luspatercept can ease a sizeable proportion of patients of their dependence on blood transfusions, and after a strong showing in phase II any substantial slip in efficacy will be taken poorly.

Product	Luspatercept	
Company	Celgene	Acceleron
NPV	$3.7bn	$1.8bn
NPV as % of mkt cap	7%	112%
Event	Phase III data due mid-year	

Sales forecasts and Acceleron’s market value suggest that pretty big things are expected of luspatercept. *EvaluatePharma*’s consensus of sellside forecasts sits at $874m in 2024, while the Massachusetts biotech boasts a market cap of $1.6bn. Acceleron will receive tiered royalties on launch in the low-to-mid 20% range, and has the right to co-promote the product in the US.

While sales at this level this might not move the needle much for Celgene, after a spate of pipeline stumbles, investors are in no mood for further bad news (*Celgene trades close to its doomsday scenario, May 22, 2018*).

Acceleron and Celgene are initially going after a poorly served population – those with anaemia caused by chronic diseases, but who do not respond to existing options. Current drug therapy includes erythropoiesis-stimulating agents (ESAs) like Epogen or less commonly Revlimid, all used off-label; only half of patients find them suitable. This leaves regular blood transfusions the only option. Luspatercept is administered via subcutaneous injection three times a week, presenting a substantially more convenient option.

Acceleron describes the drug as an erythroid maturation agent. It targets specific TGF-beta proteins involved in late-stage red blood cell differentiation and maturation, and would represent an entirely new mechanism of action in this field.

Results so far have been encouraging. At last year's Ash conference the latest cut of data from an ongoing phase II MDS trial found that more than half of treated patients had an erythroid response – improvements in their red blood cells – and more than 40% remained free of blood transfusion for an eight-week period.

Phase II luspatercept results in myelodysplastic syndrome			
Response rates	**Erythroid response**	**Transfusion independence***	**Median duration of response**
All patients	53% (52/99)	43% (29/67)	19 months
RS+	65% (40/62)	52% (22/42)	
Non-RS	34% (12/35)	30% (7/23)	
Phase II results in beta thalassemia (transfusion-dependent)			
Response rates	**Transfusion burden reduction (wks 37-48)**	**Transfusion burden reduction (wks 13-24)***	**Median duration of response**
All patients	46% (11/24)	69% (22/32)	14.2 months
*Notes: RS = ring sideroblast. * = Primary endpoint of pivotal studies. Source: MDS data Ash 2017, beta thalassemia data EHA 2017.*			

The pivotal MDS study Medalist is also looking at these measures and has recruited RS-positive patients – those with a type of anaemia in which the bone marrow produces ringed sideroblasts (RS) rather than healthy red blood cells.

A look at the phase II data shows why this has been done. RS-positive patients account for around half of MDS patients, but efficacy is greater in this subgroup. A shot at the broader MDS population is being taken with the front-line Commands trial, due to start soon.

Perhaps the decision to focus on the RS-positive subgroup is a signal that the partners expect lower response rates when Medalist reads out. Acceleron executives said earlier this month that they would consider a 27%-39% transfusion independence response as a win. Some analysts have written that a 25-30% response rate should still lead to uptake.

Investors would likely be disappointed with a result at the low end of these ranges, however – particularly as this would bode poorly for the bigger population being tested in the Commands trial which, based on phase II data, is likely to yield lower numbers anyway.

The placebo arm is expected to perform very poorly in Medalist so presumably the trial could still succeed statistically even if the response rate drops. And because these patients are so poorly served luspatercept could probably still win approval – though sales forecasts would likely be much curtailed.

Believe

Hopefully that eventuality will not unfold and response rates will remain similar to the phase II data, with no safety signals emerging. No serious red flags have been raised so far though given that the exact mechanism of action of luspatercept is unknown, and that the TGF-beta superfamily are involved in many repair mechanisms, safety readouts will be closely scrutinised.

The Believe trial in beta thalassemia should also report at the same time and much the same applies – investors will be keen to see response rates hold up.

Success is a big deal for both partners. Acceleron is built on a pipeline of TGF-beta projects, while Celgene has picked up the bill for the luspatercept R&D work since 2013. Analysts reckon that failure could slice three-quarters from the small drug developer's valuation, while even Celgene would take a hit.

Given the pessimism around the beleaguered big biotech at the moment, another high profile setback would probably have ramifications beyond the share price.

Late-stage luspatercept programme				
Trial	**Setting**	**Status**	**ID**	**Estimated patient population**
Medalist	Lower-risk MDS, second line, RS+	PIII top-line results mid-year	NCT02631070	40,000
Believe	Beta thalassaemia, transfusion-dependent	PIII top-line results mid-year	NCT02604433	20,000
Commands	Lower-risk MDS, first-line vs EPO	PIII to start this year	TBD	20,000
Beyond	Beta thalassaemia, transfusion-independent	PII ongoing	NCT03342404	20,000
-	Myelofibrosis	PII ongoing	NCT03194542	15,000
Pace-MDS	Low-risk MDS, single arm study	PII ongoing	NCT01749514	
Source: Company statements				

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