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Roxadustat passes Alps test but has bigger mountains to climb

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Fibrogen’s roxadustat has its first European win from the Alps trial, but the most important event is still to come.

Fibrogen has a lot riding on pivotal data for roxadustat, its project for anaemia in chronic kidney disease. Today's win in the European Alps trial will help its cause – but a safety analysis of the global pivotal programme, due in early 2019, is what investors are really waiting for.

Astellas, which has partnered the project in Europe and Japan, did not give many details about the Alps study, except to say it had met its primary endpoints, haemoglobin response rate in the first 24 weeks and haemoglobin change from baseline at weeks 28 to 52. Crucially, there did not appear to be any safety signals.

Leerink analysts noted that roxadustat’s efficacy now looked “more or less certain”. Trials in China and Japan have already read out positively, and an approval decision in China is expected by the end of the year. But the main questions over the asset now involve its side-effect profile.

The current standard of care for anaemia in chronic kidney disease is erythropoiesis-stimulating agents (ESAs), synthetic versions of erythropoietin that spur the patient’s bone marrow to produce red blood cells. However, these drugs are linked with thromboses and cardiovascular events.

HIF-PH inhibitors like roxadustat are designed to stabilise the HIF complex and stimulate endogenous erythropoietin production, effectively mimicking the body’s reaction to high altitude. It is thought that, compared with ESAs, they could lead to lower but more consistent blood erythropoietin levels, thus having better cardiovascular safety.

This theory will be put to the test when the full phase III programme for roxadustat reads out. Two more European trials are set to report, while five trials are ongoing in the US, where the project is partnered with Astrazeneca.

Roxadustat's pivotal programme					
Trial	**Population**	**Geography**	**ID**	**N**	**Data due**
Alps	Non-dialysis dependent	OUS	NCT01887600	597	Reported
Dolomites	Non-dialysis dependent	Europe	NCT02021318	616	Year end 2018
Pyrenees	Dialysis dependent	Europe	NCT02278341	838	Year end 2018
Himalayas	Dialysis dependent	US & ROW	NCT02052310	900	Year end 2018
Sierras	Dialysis dependent	US	NCT02273726	820	Year end 2018
Rockies	Dialysis dependent	US & ROW	NCT02174731	2,133	Year end 2018
Andes	Non-dialysis dependent	US & ROW	NCT01750190	922	Year end 2018
Olympus	Non-dialysis dependent	US & ROW	NCT02174627	2,781	Year end 2018
Source: EvaluatePharma, Clinicaltrials.gov.					

Initial data from the rest of the pivotal programme are expected by the end of the year, while a pooled safety analysis on major adverse cardiovascular events (MACE) is due in early 2019. Readout was delayed earlier this year (*More patience needed for novel anaemia class's biggest test, February 28, 2018*).

Getting a clean safety label will be particularly important if roxadustat is to be used in the less sick non-dialysis-dependent kidney disease population, which the Leerink analysts forecast will account for 45% of the drug's sales. They put peak roxadustat revenues at $5.8-8.1bn, depending on the drug's performance on MACE.

If roxadustat ends up with a similar label to the ESAs, the former's greater convenience as an oral drug could help it gain market share in the non-dialysis population, Bernstein analysts believe. Still, the emergence of biosimilar ESAs would make this tough. Realistically, roxadustat needs to show a better safety profile to have a chance of meeting the high expectations set by the sellside.

Roxadustat is not the only HIF-PH inhibitor in town. Akebia's vadadustat and Glaxosmithkline's daprodustat are also in phase III trials, but data are not due until the end of next year at the earliest. This should give Fibrogen and its partners a chance to make the most of their first-mover advantage – if they can get a good safety result.

Other HIF-PH inhibitor pivotal trials					
Trial	**Population**	**Geography**	**ID**	**N**	**Data due**
Vadadustat (Akebia) trials					
Inno2vate-Conversion	Dialysis dependent	US & ROW	NCT02892149	2,800	Q4 2019/Q1 2020
Inno2vate-Correction/Conversion	Dialysis dependent	US & ROW	NCT02865850	400	Q4 2019/Q1 2020
Pro2tect-Conversion	Non-dialysis dependent	US & ROW	NCT02680574	2,100	Mid-2020
Pro2tect-Correction	Non-dialysis dependent	US & ROW	NCT02648347	1,600	Mid-2020
Daprodustat (Glaxosmithkline) trials					
Ascend-D	Dialysis dependent	US & ROW	NCT02879305	3,000	2020
Ascend-TD	Dialysis dependent	US & ROW	NCT03400033	402	2020
Ascend-ID	Patients initiating dialysis	US & ROW	NCT03029208	300	2020
Ascend-ND	Non-dialysis dependent	US & ROW	NCT02876835	4,500	2020
Ascend-NHQ	Non-dialysis dependent	US & ROW	NCT03409107	600	2020
Source: EvaluatePharma, Clinicaltrials.gov.					