FibroGen, Inc.

The Next Big Biotech Blow-Up

November 4, 2019

Founded in 1993, FibroGen is a $3.7bn pharmaceutical company whose market value stems primarily from its flagship drug roxadustat. Roxadustat is part of a new class of drugs called hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PH inhibitors). HIF-PH inhibitors induce a hypoxia-like signal in the body that triggers hypoxia-inducible factor (HIF) activity, which leads to red blood cell production.

Roxadustat and other HIF-PH inhibitors are being promoted as a replacement for erythropoietin analogs (EPO) for the treatment of anemia. There is no question that roxadustat induces erythropoiesis and can treat anemia. However, FibroGen has been mysteriously unforthcoming with the highly anticipated pooled safety results of its pivotal Phase 3 trials pitting roxadustat against EPO in the dialysis-dependent chronic kidney disease (DD-CKD) setting and against placebo in the non-dialysis dependent chronic kidney disease (NDD-CKD) setting. The key measure of safety is major adverse cardiovascular events (MACE): a composite endpoint that includes all-cause mortality, myocardial infarctions (heart attacks), and strokes. It has been shown in the CHOIR and TREAT trials that increased exposure to EPO is strongly correlated with higher MACE rates. To be approved, roxadustat must prove that it is at least as safe as EPO and placebo by achieving MACE noninferiority: a MACE hazard ratio 95% confidence interval with an upper bound < 1.3.

In its initial pooled safety data press release and in subsequent conference calls, FibroGen declined to provide MACE hazard ratios and instead claimed there was no "clinically meaningful difference" in risk of MACE between roxadustat and EPO in DD-CKD and roxadustat and placebo in NDD-CKD. FibroGen's aggregate published clinical data says otherwise: roxadustat showed large MACE and death imbalances across its published trials, with 11/983 deaths and 23/983 MACE incidents in the roxadustat groups compared to 0/419 deaths and 1/419 MACE incidents in the control groups. The rate of MACE incidents among roxadustat patients was 9.8x as high as control:

			N		Discontinuation Rate		MACE		Deaths	
Trial	Control	Duration	Roxadustat	Control	Roxadustat	Control	Roxadustat	Control	Roxadustat	Control
China Phase 3 - DD-CKD	EPO	26 weeks	204	100	42/204 (21%)	6/100 (6%)	4/204 (2%)	0/100 (0%)	0/204 (0%)	0/100 (0%)
Japan Phase 3 - DD-CKD[1]	EPO	24 weeks	151	152	32/151 (21%)	21/152 (14%)	3/151 (2%)	0/152 (0%)	2/151 (1%)	0/152 (0%)
China Phase 2 - DD-CKD	EPO	6 weeks	65	22	6/65 (9%)	0/22 (0%)	0/65 (0%)	0/22 (0%)	0/65 (0%)	0/22 (0%)
US Phase 2 - DD-CKD	EPO	6-19 weeks	108	36	13/108 (12%)	3/36 (8%)	7/108 (6%)	1/36 (3%)	3/108 (3%)	0/36 (0%)
US Phase 2b - NDD-CKD	None	16-24 weeks	145	NA	12/145 (8%)	NA	7/145 (5%)	NA	4/145 (3%)	NA
US Phase 2 - ID-CKD	None	12 weeks	60	NA	5/60 (8%)	NA	2/60 (3%)	NA	2/60 (3%)	NA
US Phase 2a - NDD-CKD	Placebo	4 weeks	88	28	12/88 (14%)	2/28 (7%)	0/88 (0%)	0/28 (0%)	0/88 (0%)	0/28 (0%)
China Phase 3 - NDD-CKD	Placebo	8 weeks	101	51	15/101 (15%)	8/51 (16%)	0/101 (0%)	0/51 (0%)	0/101 (0%)	0/51 (0%)
China Phase 2 - NDD-CKD	Placebo	8 weeks	61	30	6/61 (10%)	3/30 (10%)	0/61 (0%)	0/30 (0%)	0/61 (0%)	0/30 (0%)
Total Reported Events (#)			983	419	143/983	43/419	23/983	1/419	11/983	0/419
Total Reported Events / N (%)			983	419	14.5%	10.3%	2.3%	0.2%	1.1%	0.0%

1 In the poster discussing the Japan Phase 3 DD-CKD trial results, the authors did not provide a complete SAE breakdown, and it is possible that additional MACE incidents occurred that were not disclosed

Roxadustat's two most advanced HIF-PH inhibitor competitors (GlaxoSmithKline's daprodustat and Akebia's vadadustat) also reported significant MACE and death imbalances in favor of the control groups. Tables summarizing public clinical data for all three drugs (roxadustat, daprodustat, and vadadustat) along with sources are available in the accompanying presentation.

HIF-PH inhibitors utilize the same pathway as EPO to achieve erythropoiesis, with HIF-PH inhibitors inducing HIF activity upstream from EPO. The scientific thesis supporting HIF-PH inhibitor safety is that HIF-PH inhibitors lead to reduced overall EPO exposure relative to EPO which should theoretically reduce MACE risk. Clinical data shows that this theory is wrong—the reduced EPO exposure reported in HIF-PH inhibitor trials is vastly outweighed by the adverse pleiotropic effects of HIFs. These have long been the dirty secret of HIF-PH inhibitors, and the presentation accompanying this summary outlines more than a dozen publications implicating HIFs in hypertension, fibrosis, immune suppression, and other adverse events that likely impacted MACE.

In defense of roxadustat, FibroGen Management has pointed to MACE+ noninferiority in the DD-CKD and NDD-CKD settings. MACE+ is a safety endpoint that includes MACE as well as hospitalizations due to chronic heart failure or unstable angina. However, the "+" in MACE+ is frequently driven by anemia rather than thrombosis and is irrelevant to safety given MACE inferiority. The chief safety concern with roxadustat is drug-driven thrombotic events, not anemia. In the DD-CKD trials, FibroGen manipulated MACE+ by prohibiting IV iron (an essential part of EPO treatment that is not necessary for HIF-PH inhibitors), which manifested as a significantly higher transfusion rate for control group patients. FibroGen's study Provenzano et al 2016 quantified the impact of prohibiting IV iron: without IV iron, only 33% of EPO patients achieved Hb responses (compared to 79% of roxadustat patients) despite the investigators excluding EPO hyporesponders from enrollment. Placebo patients in roxadustat's NDD-CKD trials also experienced significantly higher rescue therapy rates—as one would expect. The higher control group anemia rates driven by trial design (using placebo comparator and banning IV iron) create misleading MACE+ hazard ratios that will not aid in drug approval.

While withholding the actual MACE hazard ratio data, FibroGen Management has trumpeted misleading statistics. FibroGen has stated that the total MACE incident count was lower in the roxadustat group compared to EPO in the pooled DD-CKD trial, which many interpreted as meaning that the MACE hazard ratio was less than 1. This is wrong: the lower numerical event count is the product of a much higher discontinuation rate in the roxadustat group. Dropouts have consistently been much higher in the roxadustat group compared to control, with the gap widening as trial duration increases (see table on prior page). In the China Phase 3 DD-CKD trial, the roxadustat discontinuation rate was 3.4x the EPO discontinuation rate. Patients who discontinue the drug are immune to MACE—but are also censored from the population and do not affect hazard ratio calculations. In a similar vein, FibroGen claimed that a "conservative" post-hoc intention-to-treat (ITT) analysis for the NDD-CKD group demonstrated non-inferiority to placebo. ITT analysis is completely inappropriate in this context because it dilutes the safety signal by including dropouts who are no longer taking the drug. Management's obtuseness strongly suggests that roxadustat missed the primary safety endpoint, and published MACE data indicates that it likely missed by a wide margin.

FibroGen is also developing pamrevlumab, an anti-CTGF (connective tissue growth factor) antibody. Pamrevlumab has been FibroGen's drug in search of a disease for years. FibroGen has run clinical trials evaluating pamrevlumab (formerly known as FG-3019) in fibrotic diseases since 2003, including multiple trials which FibroGen concluded or terminated without ever publishing results. FibroGen portrays CTGF as the central mediator of fibrosis, but the rest of the research community assigns it a minor (if any) role, with TGF-β1 implicated as the master regulator. There is no consensus that CTGF has a key role in any of the indications FibroGen is pursuing—or any diseases for that matter. We believe pamrevlumab is worthless.

FibroGen is currently enrolling Phase 3 trials for pamrevlumab in idiopathic pulmonary fibrosis (IPF) and locally-advanced pancreatic cancer (LAPC). The LAPC trial is expected to read out in 2022 while the IPF trial is expected to read out in 2023. We believe the LAPC trial has no chance of success and that even if the current IPF trial were to succeed, the drug would not make it to market for nearly a decade from today (precedent shows that a second Phase 3 trial would be required for approval) and it would be unsellable due to clinically irrelevant trial design that prohibited use of current (and likely soon to be generic) standard of care.

In a randomized controlled trial of pamrevlumab + chemotherapy vs. chemotherapy in LAPC, there was no difference in ORR between pamrevlumab + chemotherapy (21% ORR) vs. chemotherapy alone (23% ORR). PFS and OS were listed among the trial's primary outcome endpoints, but were conspicuously absent from all disclosures indicating that, like ORR, pamrevlumab showed no benefit in PFS and OS. The scientific concept behind using pamrevlumab for pancreatic cancer (targeting stromal growth) has been tried multiple times via hedgehog inhibitors and has consistently failed: see vismodegib, saridegib, and M402.

FibroGen has touted pamrevlumab in LAPC based on a data-mined nugget: the percent of patients eligible for surgical resection was higher in the pamrevlumab group compared to the control group. "Eligibility for surgical resection" is not a valid primary endpoint and FibroGen's focus on the metric is classic misdirection driven by an aberrantly low surgical resection rate in the control group that may ironically have been driven by treatment efficacy removing the need for surgical resection. As the meta-analysis Gillen et al 2010 (n=4,394) showed, the percent of pamrevlumab + chemotherapy patients deemed eligible for surgical resection in FibroGen's trial was identical to the expected chemotherapy rate in LAPC (33.2% in Gillen vs. 33.3% in FibroGen's trial).

We have serious doubts about pamrevlumab's efficacy in treating IPF due to its mechanism of action failing to demonstrate benefit in fibrotic diseases in the past and a published lack of dose response in IPF. Management appears to share our concerns: FibroGen is currently only running a single Phase 3 IPF trial now (expected to take four years) even though two Phase 3 trials would be required for approval: Ofev required two, Esbriet required three (one failed), and Galapagos is currently running two for GLPG1690 (ISABELA1 and ISABELA2). Waiting for the results of the first Phase 3 trial before initiating the second Phase 3 means that the earliest pamrevlumab could possibly make it to market for IPF would be 9-10 years from today.

FibroGen also withheld results of a placebo-controlled study designed to test whether pamrevlumab added any benefit when stacked with current IPF standard-of-care (Esbriet and Ofev). We believe the efficacy results were never published because pamrevlumab failed to show any benefit. That failure likely informed the decision to structure the Phase 3 trial as placebo-controlled with background Esbriet/Ofev prohibited. This would make pamrevlumab unsellable even if it succeeds: it would likely be competing with generic Esbriet/Ofev as well as potential new competitors which show additive benefit when combined with Esbriet/Ofev.

While FibroGen has no new clinical results expected for pamrevlumab until LAPC in 2022, judgment day for roxadustat quickly approaches: FibroGen is scheduled to present MACE results at ASN 2019 on Friday, November 8 at 2:00 PM. The public will soon discover whether FibroGen achieved the greatest (and least explicable) clinical safety turnaround of all time, or roxadustat failed to achieve MACE noninferiority and should be marked down to zero.

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