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Metsera Reports

December 18, 2023

Clinical Trial Updates

Structure Therapeutics gives clinical update on oral GLP-1RA

Summary and Implications

- Structure Therapeutics today reported Phase 2a data on its oral small molecule GLP-1RA GSBR1290 in T2DM and in obesity – share price down ~40% because of missed expectations
- Key results: weight loss appears relatively consistent with other oral GLP-1RAs (notably orforglipron), vomiting rates up to 62% likely due to weekly titration, a single case of elevated LFTs with unclear relationship to the drug
- Structure is positioning GSBR-1290 as both a monotherapy and as a backbone for combinations, and indicated that lead candidates for oral combinations (amylin, GIP, GCGR) will be selected in 2H2024 and an apelin agent for combination with GSBR-1290 has completed Ph1

Context

Structure Therapeutics is among the companies developing small molecule GLP-1RAs for oral administration. Phase 1B data were released in September (see attached). Other agents are Carmot Therapeutics' CT-996 – recently acquired by Roche, Lilly's orforglipron, and in the peptide field oral semaglutide (50 mg for obesity and 14 mg for T2DM – the latter has been

approved).

To date, efficacy and tolerability for oral options has been inferior to next-generation injectables such as CagriSema and retatrutide. That may explain why several companies, including Novo (oral amycretin), Carmot (now Roche), Structure, and others have initiated development of oral combination agents.

Content

Structure today released Phase 2a data from a 54-person T2DM study, and 8-week interim data from a 40-person obesity Phase 2a study. After the data release, Structure's shares traded ~40% lower – likely because of expectations investors had based on the shorter and smaller Phase 1 study.

Both studies were placebo-controlled – the T2DM study included a 45 mg and a 90 mg arm, and the obesity study included a 90 mg arm. An additional 24 subjects in the obesity study had a trial conduct issue and will be added for the final 12-week read-out.

Discontinuation rates were low – two subjects discontinued in the T2DM study (one due to GI issues, one due to COVID-19) and no subjects discontinued the obesity study. No study-related SAEs were reported. One patient, who was receiving treatment with atorvastatin and aspirin and was diagnosed with steatohepatitis during the study, had a notable elevation in liver enzymes, while mean liver enzyme levels were unchanged in the studies. The one instance of elevated LFTs did cause some potential concern among analysts who were primed by Pfizer's discontinuation of the -532 program due to potential liver safety issues.

Vomiting rates were dose-dependent, up to 62% in the 120 mg group. N/V appeared to be related to titration as events happened primarily early on during the treatment period. Notably, the study had aggressive weekly titration, which could at least partially explain the high vomiting rates. Approximately 40% had changes in the dosing due to tolerability issues (e.g., down-titration, dose hold)

The PBO-corrected A1c reduction in the T2DM study was ~1% at Day 84, which is less than the 1.7% reduction that was seen with orforglipron (despite the fact that the main analysis was per-protocol – i.e., those with treatment modifications were excluded). It could be speculated that additional A1c reduction would have been seen should the study have been longer in duration, and it could also be that the used doses were lower than those required for better efficacy.

Body weight loss of ~3.5% was also slightly less than in the orforglipron Ph2 T2DM study (>5% at the same timepoint). Structure indicated that an additional T2DM study will be initiated in 2H2024, which will test longer titration periods, higher doses, and possibly a new formulation in T2DM.

In the obesity Ph2a study, weight loss at Day 56 was ~5%, which is comparable to orforglipron in a similar Phase 2 study at the same timepoint – although it should be kept in mind that the GSBR-1290 trial used more aggressive titration (and hence reached higher exposure levels early on in the study). Based on the previously released Phase 1b study, investors may have expected more weight loss.

Next steps for Structure include 1) full data from the obesity Phase 2a study, 2) a study with the dual objective to switch from capsules to tablets and test longer titration intervals, 3) initiation of a 275-patients 36-week obesity Phase 2 study, and 4) initiation of a new T2DM study, as previously mentioned.

In terms of positioning, Structure seems to consider GSBR-1290 as both a competitive oral monotherapy and as a foundation for combination therapies. Structure is aiming to select lead compounds for a GIP combination as well as amylin and glucagon combinations in 2H2024. In addition, Structure is developing an apelin analog for co-administration with GSBR-1290 that would attenuate lean body mass loss – Phase 1 has been completed for the apelin (without GSBR-1290).

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