Evaluate Vantage

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# EASD 2022 – Pfizer’s oral GLP-1s struggle for a therapeutic window

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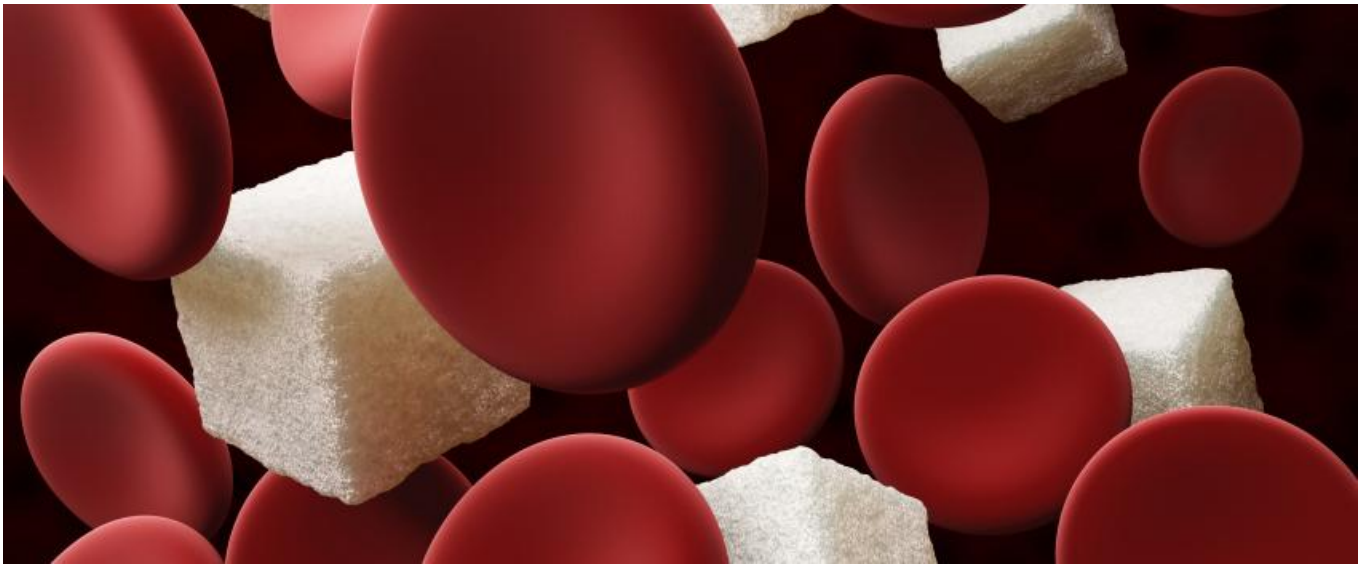


## Neither project is an obvious candidate for phase 3, so more mid-stage trials are planned.

Earlier this year Pfizer’s oral GLP-1 agonist danuglipron looked promising in diabetes. Data presented at EASD this week, however, makes rather more disappointing reading, with tolerability looking poor at the high doses and efficacy weak at the low.

Pfizer is hedging its bets and has yet to decide whether to take danuglipron or a backup GLP-1, still in phase 1, forward. That asset, PF-07081532, will enter phase 2 by the end of the year, management said on a call last night. Phase 2 trials of danuglipron in non-diabetic patients are likely to conclude later next year. Only then will a candidate be selected for phase 3.

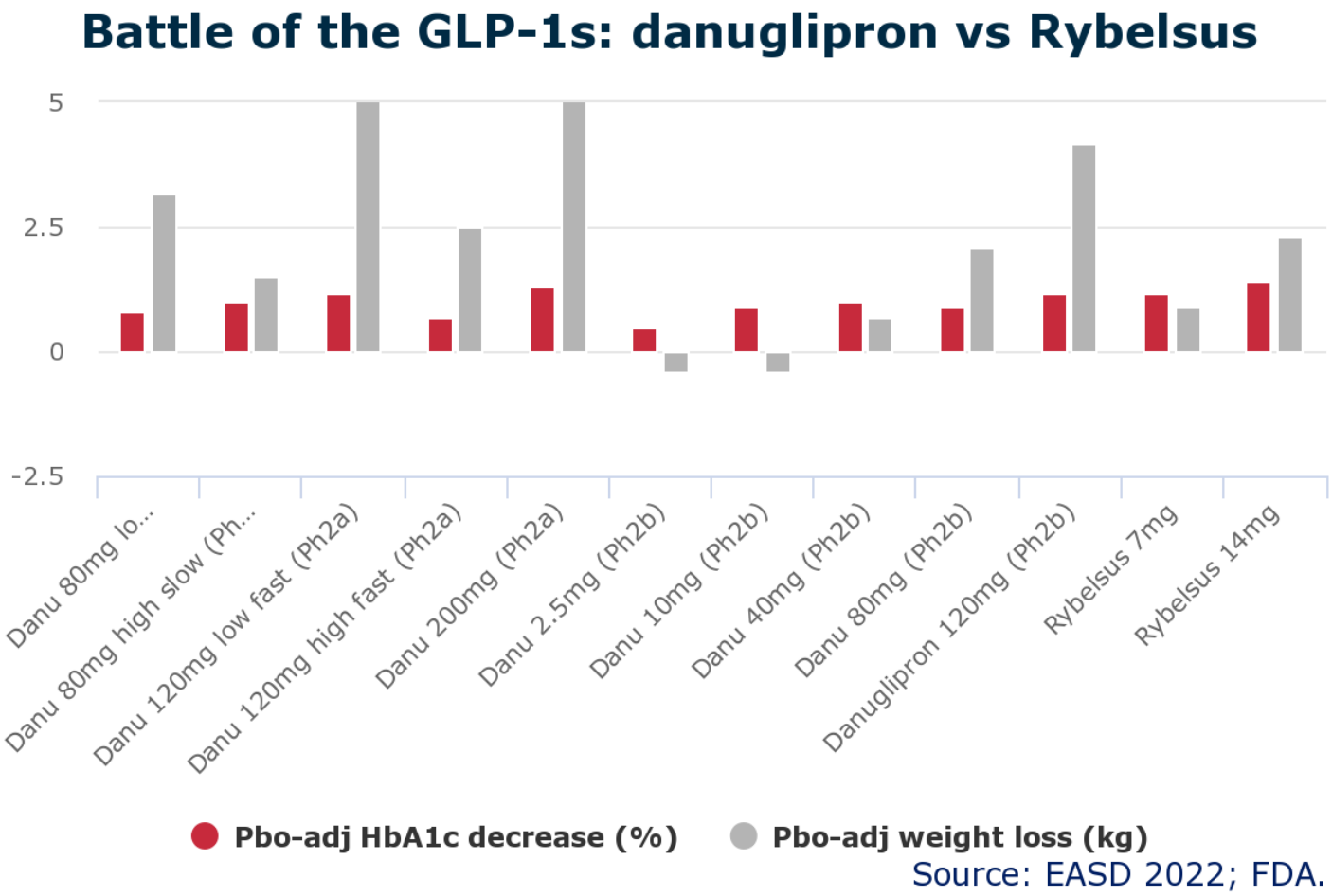
This cautious approach means that Novo Nordisk, whose oral GLP-1 agent Rybelsus is already on the market, need have no immediate fear of an oral challenger.

The other oral project to watch is Lilly's LY3502970, which had phase 1 data at EASD but has already started phase 2.

**First up**

Pfizer’s data presented at the EASD meeting came from two mid-stage trials: a US phase 2a and a worldwide phase 2b, both in patients with type 2 diabetes. The phase 2a trial also enrolled a small cohort of patients with obesity and without diabetes; these patients were evaluated for safety but not efficacy.

If efficacy alone is considered, the higher doses of danu, also known as PF-06882961, look better than Rybelsus on a cross-trial basis, at least on weight loss. On blood sugar reductions, though, none of the danu doses matched the placebo-adjusted 1.4% seen with the higher approved dose of Rybelsus.




*The chart above concerns diabetes patients only. Danu data from Ph2a (NCT04617275) at 12wk and Ph2b (NCT03985293) at 16wk. Rybelsus data from Ph3 Pioneer-1 (NCT02906930) at 26wk. In the ph2a trial, danu was titrated using a low (5mg BID) or high (10mg BID) starting dose, and slow (2wk) or fast (1wk) titration steps.*

**Side effects**

Add in the safety findings and danu comes off particularly poorly.

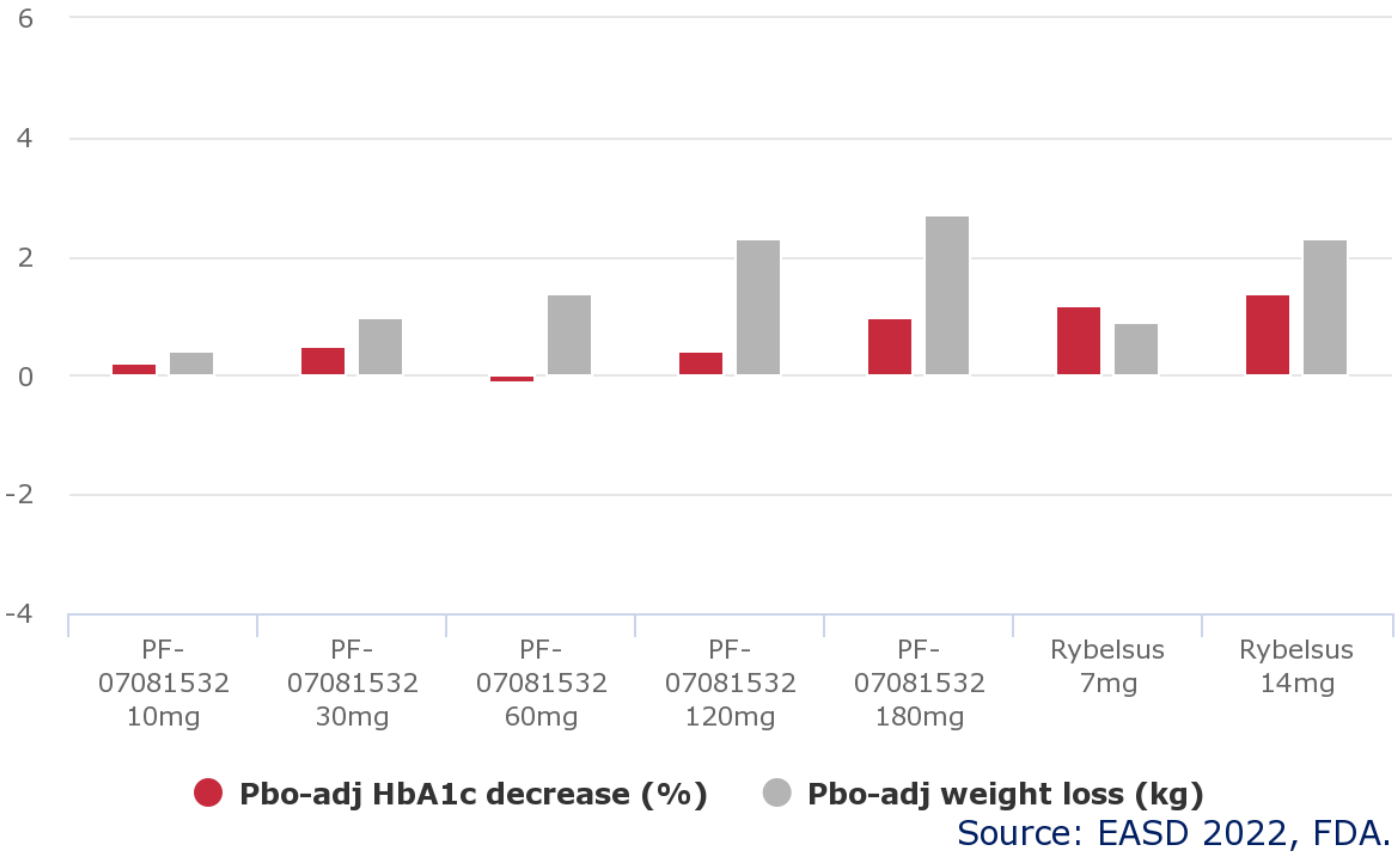
The higher doses, 80mg-200mg twice-daily, were not well tolerated, with vomiting and diarrhoea seen in up to 29% and 22% of diabetes patients, respectively, in the phase 2a trial. Since these are the only doses that can hold a candle to Rybelsus, finding a therapeutic window could be tricky.

And among the patients with obesity, tolerability was also an issue: 46% experienced vomiting after treatment with danu 200mg HF, though only 5% had diarrhoea. This will surely raise questions about future indication expansion for Pfizer's project.

Perhaps Pfizer will instead opt to take forward PF-07081532, its oral GLP-1R agonist. This has a slight edge over danu in that it is given just once daily; this is balanced, of course, with its earlier stage of development.

Data presented at EASD from its phase 1 trial in 51 diabetes patients suggest that this asset might not be as powerful as danu at the doses tested, with the highest dose reducing blood sugar by 1% over placebo, and weight loss by 2.7kg.

## Battle of the GLP-1s: PF-07081532 vs Rybelsus




Source: EASD 2022, FDA.

*The chart above concerns diabetes patients only. PF-07081532 data from Ph1 trial (NCT04305587) at 4-6wk. Rybelsus data from Ph3 Pioneer-1 (NCT02906930) at 26wk.*

Like danu, ’1532 beat Rybelsus on weight loss but not blood sugar, though the much earlier time point must be taken into consideration; perhaps performance will improve with longer treatment.

And tolerability was notably poor. Nausea hit 88% at the highest dose, with vomiting seen in 38% of patients and diarrhoea in 50%. Pfizer has very little room to manoeuvre, though on a conference call yesterday the company did say that it planned to use slower titration schemes in its longer duration studies to improve tolerability further.