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Crenezumab fails to live up to its limited billing

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At least in Roche's strategy to tackle Alzheimer's disease the Swiss group has the luxury of choice, since on the basis of the phase II data released yesterday crenezumab is going nowhere fast.

Some borderline subgroup analyses notwithstanding, what little hope might have existed for the antibody looks to have been dashed by negative results from two long-awaited phase II trials. Whether this strengthens or weakens the case for a similarly acting project, gantenerumab, will be a question that followers of the amyloid-beta hypothesis will now try to answer.

For now, however, the crenezumab data look like another nail in the amyloid-beta approach that has seen Elan's bapineuzumab and Lilly's solanezumab fail in large phase III programmes, though Lilly is pressing on with a newly designed pivotal trial in early-stage Alzheimer's.

If the approach has any hope of succeeding it is surely in these early patients. This much was demonstrated by crenezumab in its two phase II trials, Abby and Blaze; both recruited mild to moderate rather than just mild Alzheimer's patients.

Abby, being a larger trial with co-primary endpoints in cognition and function, was the more important of the two. In the all-comer population crenezumab failed to reduce the decline in either the Adas-Cog or CDR Sum of Boxes scales versus placebo, Roche said at the Alzheimer's Association International Conference this week.

As such the group had to rely on subgroup analyses, but here too there was little to shout about. Looking at just the higher of two doses in just the mild population – a pre-specified analysis – there was a numerical difference favouring crenezumab, but this failed to hit statistical significance (p=0.13).

A p value of 0.036 was hit in cognitive decline reduction in an even milder cut of the population, but the value is not adjusted for multiplicity, and in any case this was a post hoc analysis so holds no statistical rigor.

Clutching at straws? Crenezumab phase II analysis		
	Abby	**Blaze**
Trial ID	NCT01343966	NCT01397578
Intent-to-treat population	431	91
Reduction in Adas-Cog 12 decline	numerical benefit*	not disclosed
Reduction in CD-SOB decline	no benefit*	not disclosed
Biomarker effect	not disclosed	not disclosed*
Adas-Cog benefit (high dose)	16.8% (p=0.19)	10.3% (p=0.84)
CD-SOB benefit (high dose)	3.1% (p=0.85)	7.4% (p=0.84)
Adas-Cog benefit (mild disease + high dose)	23.8% (p=0.13)**	52.0%***
CD-SOB benefit (mild disease + high dose)	–1.0% (p=0.96)**	41.5%***
Adas-Cog benefit (even milder disease)	35.4%***	not disclosed
CD-SOB benefit (even milder disease)	19.6%***	not disclosed
Safety	Pneumonia in 3.2% of crenezumab patients vs 0.6% on placebo	
**primary endpoint; **pre-specified subgroup; ***post-hoc analysis*		

Roche said it would present primary endpoint results from the smaller Blaze trial, relating to brain amyloid load, at a later meeting. Cognition and functional measures – secondary endpoints – favoured crenezumab non-significantly, and to a greater extent in the mild population, though this too was a post hoc dredge.

Unlucky?

Perhaps the group was unlucky in that it could not learn from the phase III bapineuzumab and solanezumab failures, as Abby and Blaze were already under way when these occurred. Likewise, it was only last year that the FDA strongly backed the targeting of early forms of dementia (*Roche set to benefit from FDA effort to tackle Alzheimer's paradox, February 8, 2013*).

However, Deutsche Bank analysts did expect the data to be positive enough to continue crenezumab development – something that is up in the air now that crenezumab looks to be Roche's third clinical failure of 2014, after bitopertin in schizophrenia and Metmab in lung cancer.

The group is vague about future plans, but both it and AC Immune, crenezumab's originator, stressed the agent's potential in early disease. This gives some support for Lilly's latest phase III plan for solanezumab, though analysts from Societe Generale were dismissive today, writing: "the failure of a third drug ... suggests that targeting the beta-amyloid pathway may not be a fruitful approach".

Certainly Lilly will be hoping that this is not the case, as will the likes of AstraZeneca and Merck & Co, which are working on BACE inhibitors, a mechanism based on the concept of reducing circulating beta-amyloid protein.

Were crenezumab Roche's only Alzheimer's hope the group might feel pressured to continue in Lilly's tracks. However, the Swiss company is also working on Evotec's early-stage MAO-B inhibitor RG1577, and – most importantly – gantenerumab.

The two phase III studies of this second beta-amyloid antibody are focusing on mild disease and prodromal Alzheimer's, an early form of dementia. While crenezumab might now be a loss for AC Immune, with gantenerumab Roche looks to be on somewhat safer ground.

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