Please also respond to these additional comments by the committee:

Main paper:
Revision nicely done and much easier read for a clinical audience.

Thank you.

Abstract will need to be submitted in standard format. Intro, methods, results, conclusion.

We have revised the abstract.

Indicate on figures which direction is associated with improved cognition.

We have revised the figure 2 in the main text, as well as figures in the supplemental information and in the web application. All figures now say “Amyloid reduction harmful” to the left of the dotted line, and “Amyloid reduction helpful” to the right of the dotted line.

Pg 13 line 37: amyloid-β by a specific mechanism will slow cognitive change slows cognitive change while amyloid reductions
--repeat words.

We have edited this text to remove repeated words.

Discussion is a bit long:
First part of discussion should be condensed into a single paragraph recapitulating your findings. The first paragraph of your strength and limitations section might be a nice way to go about this first summary paragraph.

We have significantly shortened and revised the discussion. The first part of the discussion is now a single paragraph and other sections have been shortened as well.

Might move the information on cautious interpretation to later in the discussion.

We have moved this section to later in the discussion.

And it might be simple enough to state that findings may be attributable to chance--using the binomial distribution to calculate a probability of "significant" finding under the null might be beyond the scope this clinically focused article (although I do sincerely appreciate the calculation).

We have removed this calculation.

Please add dissemination plan; even if this included getting traction on twitter, etc.

We have added the following dissemination plan:
“Results will be disseminated using social media (Twitter), at conferences (Alzheimer’s Association International Conference, Methods in Longitudinal Dementia Research, and Society for Epidemiologic Research), and to stakeholders at non-profit organizations. We plan to disseminate findings to the general public in a press release.”

Please move the PPI statement to the results section

We have moved the PPI statement to the results.

Fast Facts:
I enjoyed reading your fast facts piece. While I think it is well written, is it possible to make it more generally useful? There is a heavy reliance on using your main manuscript as an example. In some cases using your paper as illustrative is quite appropriate, but in others, such as the 'When and why to use' section, the heavy reference to Your manuscript is less generalizable. Please let me know if you need clarification on this point.

We have significantly revised the fast facts piece to make it more generalizable. We have removed significant sections specific to our paper, and use evaluating the effect of amyloid on cognition only as an illustrative example.

Please bolster the limitations section with this information that you've included in the main paper:

"The pooled result across all trials is relevant if the effect of reducing amyloid on cognition does not vary with mechanism by which amyloid-β is targeted, i.e. by drug

Targets outside of the proposed mechanism would be attributed to the posited causal pathway did not account for the covariance between measured cognition and measured SUVr that might be induced if other factors influence amyloid"

We have added the above limitations to the fast facts piece:

“There are limitations to this type of analysis. The pooled result across all trials is easily interpreted only if the effect of changing the biological target on the outcome does not vary across medications. This analysis assumes that the drug has no influence on the outcome that is not mediated by the biological target. By making the effect estimates directly comparable, this analysis will nonetheless help identify drugs that may influence the outcome via mechanisms unrelated to the target. Due to data limitations, it may not be possible to account for the covariance between the biological target and the outcome that might be induced by common causes of both. Finally, this analysis requires postulating the timeframe on which the biological target influences the outcome.”