Author’s response to reviews

Title: Synthetic high-density lipoprotein nanoparticles for the treatment of Niemann-Pick Diseases

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We appreciate the positive responses to our revision from all four reviewers. In addition, we modified our manuscript in response to comments from Reviewer #3 as follows:

Reviewer #3: The authors have responded constructively to the initial review and have addressed most of my concerns. The one remaining concern is point #5. With respect to the response of the liver to the 5A-SM, the data would suggest that cholesterol is being mobilized from the liver (increased HMGS expression) and increased serum lipoprotein cholesterol, and the new data suggests that their is reduced inflammation. What most readers will want to know is whether these changes were also accompanied by reduction of lysosomal cholesterol and sphingolipids or oxysterol biomarkers, which would speak to amelioration of the NPC liver phenotype. Inclusion of this data - positive or negative - would strengthen the manuscript.

We completely agree with the reviewer’s comment that this would be important information to include, if available. Unfortunately, we do not know whether 5A-SM treatment reduced lysosomal cholesterol or sphingolipid storage in liver or normalized oxysterol biomarkers. We had attempted to address the question of effects on lysosomal cholesterol storage by filipin staining of liver sections, but found the results to be quite variable and inconclusive, indicating that an alternative analytic technique will be needed to answer this question. We agree that these are important issues to address, particularly as optimized treatment regimens are tested in additional, long-term in vivo studies. As such, we have added the following statements to the Discussion (lines 650-655):

“5A-SM treatment of Niemann-Pick C mice induces cholesterol mobilization from the liver (increased HMGCS expression, Fig. 5c), increases serum cholesterol (Fig. 5a), and reduces liver inflammation (Fig. 5f). These data set the stage for additional analyses in Niemann-Pick animal models, including comparisons with other therapies currently administered to patients or in clinical trial. Future analyses are also needed to determine the extent to which optimized sHDL treatment regimens impact lysosomal cholesterol and sphingolipid storage in liver and normalize oxysterol biomarkers.”