Additional Materials

This supplementary information section summarizes previous quantitative findings on 153 MCI & AD patients involved in the short (4 months) and long-term (12 months) administration of intra-nasal insulin using the ViaNase device to deliver the drug. It also provides information on the 22 patients involved in the long-term (3 years plus) compassion use of ViaNase device delivered intra-nasal insulin [5, 6, 7]. The first randomized, placebo-controlled pilot study of ViaNase delivered intra-nasal insulin consisted of 104 adults with amnestic mild cognitive impairment (n = 64) or mild to moderate AD (n = 40); all of whom were treated with 20 and 40 IU daily dosages of intra-nasal insulin for 4 months [9]. The mean patient age was 71 years old, and the mean 3MSE score was 83.7-84.3 [20 IU/40IU]. 50-57% were positive for the high-risk apolipoprotein E epison-4 allele. The following results were reported: "Treatment with 20 IU of insulin *improved delayed memory* ($P < .05$), and both doses of insulin (20 and 40 IU) *preserved caregiver-rated functional ability* ($P < .01$). Both insulin doses also preserved general cognition as assessed by the ADAS-cog score for younger participants and functional abilities as assessed by the ADCS-ADL scale for adults with AD ($P < .05$). Cerebrospinal fluid biomarkers did not change for insulin-treated participants as a group, but, in exploratory analyses, changes in memory and function were associated with changes in the Aβ42 level and in the tau protein–to–Aβ42 ratio in cerebrospinal fluid. Placebo-assigned participants showed decreased fludeoxyglucose F 18 uptake in the parietotemporal, frontal, precuneus, and cuneus regions and insulin-minimized progression". The second placebo-controlled study of ViaNase delivered intranasal insulin administration consisted of 49 of 289 patients with mild cognitive impairment (MCI) or mild Alzheimer's disease (AD) who were randomized to receive either insulin or placebo daily for 12 months (SNIF 2018).[1] This was a Phase 2/3 trial at 26 US sites and a change in cognitive function from baseline to 12 months served as the primary endpoint; with the primary outcome measure the Alzheimer's Disease Assessment Scale-Cognition measure (ADAS-Cog 12). The ViaNase delivered intra-nasal insulin *slowed the annual progress of cognitive decline by 50%*--or only a 2.5 point decline per patient on the ADAS-Cog12 versus the 5 point decline per patient of the placebo group. This significant "separation was evident at 3 months and continued to widen over the course of the [12 month] study" [77]. Finally, qualitative findings from an

[1] Assessments were made at baseline and at three-month intervals until the end of the study, when participants were offered open-label insulin treatment for another 6 months. The other 240 patients used a different device (Precisions Olfactory Delivery [POD]) which failed to produce any difference in outcome on the ADAS-Cog 12 measure at 12 months with the placebo group (CTAD 2018). Both POD and placebo groups increased by about 4 points on the ADAS-Cog 12 measure, indicating worsening. Nor were there any changes in any other Alzheimer's-related biomarkers like amyloid-beta 40 and 42, total tau or phosphorylated tau (*Clinical Neurology News* 12/4/18:2). The model controlled for age, sex, genetic risk status and investigation site. Patient were a mean of 71 years old, with a mean Mini Mental State Exam score of 25. Around 42% were positive for the high-risk apolipoprotein E epison-4 allele.

open label study of 22 MCI and AD patients on the 3 year plus compassionate use of intra-nasal insulin are also reported.[2] These patients displayed, before ViaNase delivered treatment, significant symptoms of social and linguistic withdrawal, flattening of affect and irritability as well as moderate to high levels of family-reported care-giver stress [5, 6, 64]. Several publications extensively document treatment-mediated improvements in language, visuospatial and, in particular, executive functioning test scores of patients at moderate AD and an early MCI patient [5] and a return of pragmatic competence in the areas of jokes, self-expression and empathy in early and moderate AD and MCI patients [6, 64]. Over 90% of caregivers of the 22 compassionate use patients also reported moderate to very strong reductions in caregiver stress after one year of intra-nasal insulin administration to their family members [6, 64, 78, 79].

[2] These MCI & AD patients live in naturalistic settings (2011-present) and provide linguistic evidence on phenomena as they naturally occur, i.e. they provide conversational data for the case-study methodology as used by sociologists for the purpose of theory development and building [75]. Hamilton [38] and Causino Lamar et al. [76] found that it is only in such conversations that it is possible to describe the full range of communicative competence of a person with AD.