Smell Function Testing and Alpha-Synuclein Seed Amplification Assay for Inclusion and Stratification – in a Clinical Trial of Exidavnemab in Parkinson's Disease and Multiple System Atrophy

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Introduction

Exidavnemab is a monoclonal antibody targeting aggregated forms of alpha-synuclein, and it is critical that clinical trials with exidavnemab include participants with the targeted pathology. While the CSF alpha-synuclein seed amplification assay (SAA) test is a highly accurate tool in distinguishing participants with alpha-synuclein pathology from those without, it was applied for stratification rather than inclusion in the ongoing Phase 2a trial for exidavnemab in Parkinson's disease (PD) and multiple system atrophy (MSA) (EXIST, NCT06671938), due to the current lack of in vitro diagnostic certification for the test in Europe.

Exidavnemab Mechanism of Action

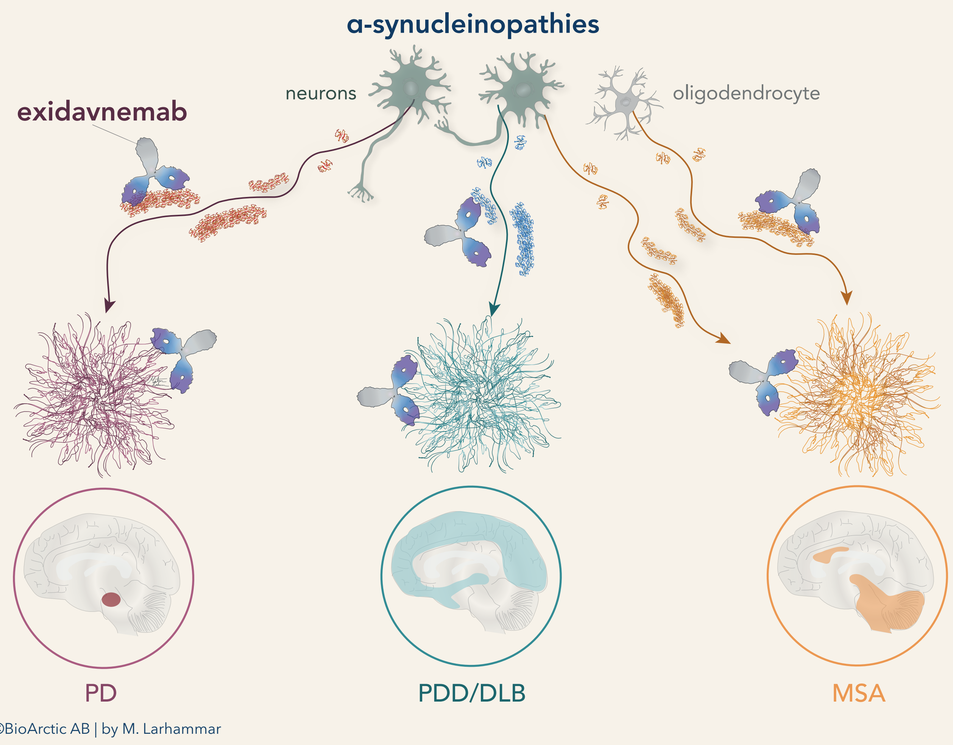

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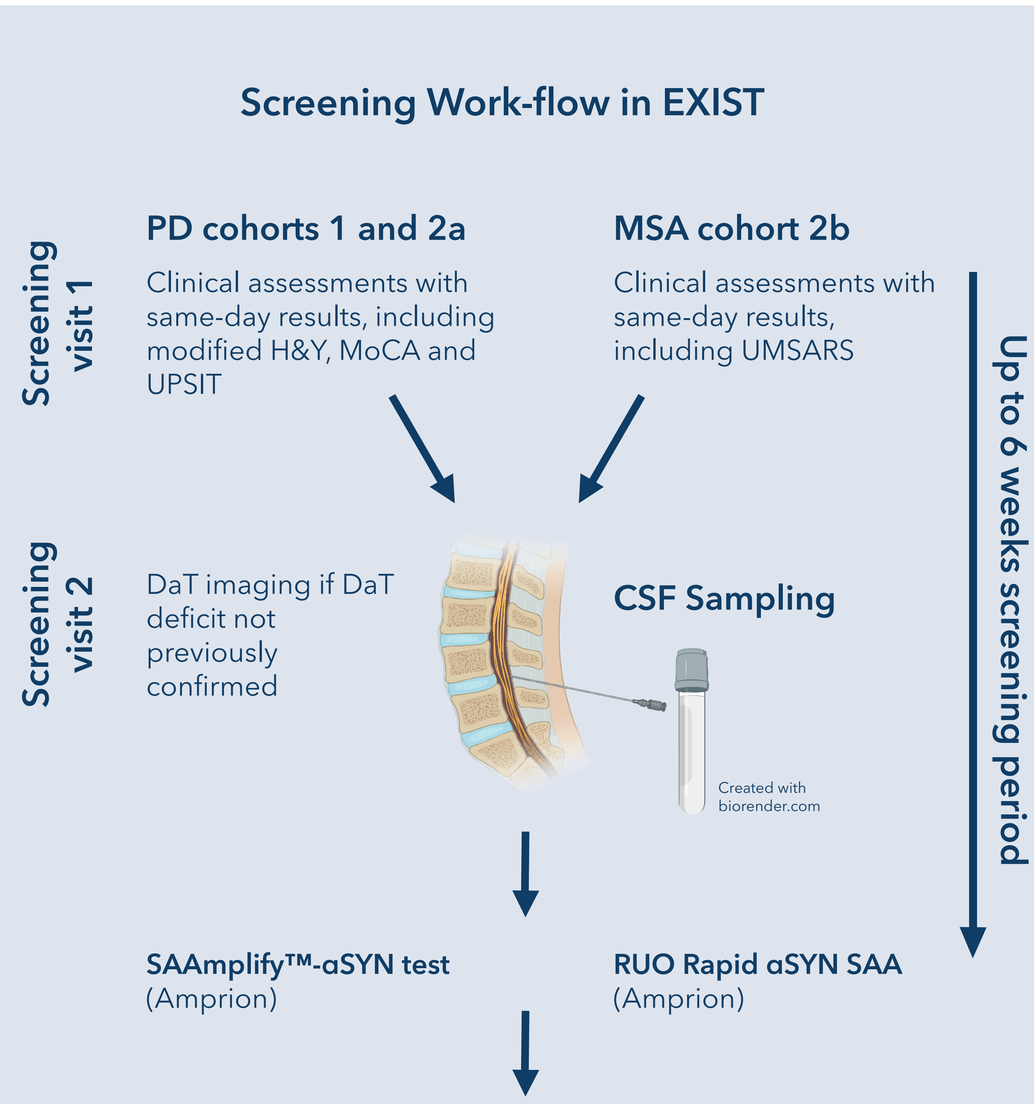
Figure 1. Exidavnemab targets aggregated forms of alpha-synuclein with potential to intervene in the spread of pathological aggregates in both MSA and in neuronal synuclein disease, i.e. PD, PD dementia (PDD) and dementia with Lewy bodies (DLB).

Participant Age	Male	Female
More than or equal to 80 years	≤18	≤23
75 to79 years	≤21	≤24
70 to 74 years	≤23	≤27
65 to 69 years	≤25	≤28
60 to 64 years	≤26	≤30
55 to 59 years	≤28	≤32
Less than or equal to 54 years	≤31	≤32

Table 1. Age and sexadjusted cutoff scores on the UPSIT applied for inclusion in PD cohorts of the EXIST trial. The UPSIT comprises 40 odorant strips. For each strip, participants are required to identify the correct smell from a forced choice of 4 possible answers[1]. Note: The UPSIT must be repeated if the participant has present symptoms of rhinitis.

Screening Work-flow in EXIST



- Results reported back to sites
- Eligible participants randomized with stratification on SAA status

Figure 2. To enrich the EXIST trial for participants likely to be positive on the SAA test, we implemented a screening approach for PD participants with reduced smell on the University of Pennsylvania Smell Identification Test (UPSIT) as a requirement for inclusion. CSF SAA testing (SAAmplify™-αSYN test) was only performed on PD participants qualified based on the UPSIT. MSA participants were not prescreened with the UPSIT test, as for this indication pathological spread in CNS does not have the olfactory bulb as an initial area of pathology and hence the UPSIT is not applicable as a screening tool for the likelihood of SAA positivity[2]. CSF SAA status was used for stratification in all three cohorts.

Summary

The screening outcome shows that pre-screening on the UPSIT followed by CSF SAA testing can be successfully applied in clinical trial practice with reasonable screening timelines. While literature shows that pre-screening in PD participants with UPSIT can reduce the number of SAA negative participants in trials[3, 4], the screening outcome also demonstrates that the use of SAA positivity as an inclusion criterion cannot readily be replaced by screening on DaT deficit and smell function. Where CSF SAA positivity is applied as an inclusion criterion, the UPSIT remains a practically applicable tool for prescreening that is likely to meaningfully reduce the number of lumbar punctures performed to screen out SAA negative PD participants.

Cohort	1	2a	2b
Indication	PD	PD	MSA
Participants, n	13	13	12
Age, mean years (SD)	57.3 (9.3)	65.9 (8.0)	64.4 (7.0)
Male, n (%)	9 (70%)	11 (85%)	5 (42%)
Female, n (%)	4 (30%)	2 (15%)	7 (58%)
Disease duration, mean years (SD)	2.5 (1.6)	2.5 (1.3)	0.6 (0.6)
UPSIT score, mean (SD)	21.8 (6.5)	19.7 (4.7)	Not applicable
SAA positive, n (%)	13 (100%)	10 (77%)	11 (92%)

Table 2. Patient characteristics of participants included in the EXIST trial. In the first PD cohort (Cohort 1), 13 of 14 participants subjected to the UPSIT during screening were positive for reduced smell and proceeded to lumbar puncture. All 13 individuals included in Cohort 1 had a positive SAA status. In the second PD cohort (Cohort 2a), all 13 participants subjected to the UPSIT were positive for reduced smell, and 10 of 13 were SAA positive. Participants in Cohort 2b were not subjected to the UPSIT. In this cohort, 11 of 12 randomized participants were SAA positive. The full screening, including CSF SAA testing, was completed within the 6-week screening period for all participants.

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