CLINICAL DEVELOPMENT PLAN
(for the purpose of AXON 0,00/20)

Phase I clinical study with AADvac1 and the open-label follow-up study were completed and AADvac1 has entered the next phase of its clinical development in various target indications and with expanded study objectives. A randomized, placebo-controlled, parallel group, double-blind, multi-center, multinational phase II study to assess safety and efficacy of AADvac1 in Alzheimer's disease (AD) was completed in Q3 2019.

AXON Neuroscience is now running:

(i) a randomised parallel group single-blind multi-centre **phase 1 pilot study** of AADvac1 in patients with non-fluent primary progressive aphasia (nfppA).

Completion of phase II clinical study will enable AXON Neuroscience to correctly set-up and plan next phases of clinical development focused either on a confirmatory phase IIb clinical study or directly a phase III clinical study, which, if successful, will lead to a final marketing authorization of AADvac1.

All new drug products must be approved by the respective regulatory agency governing the respective market before a particular product can be introduced into the market. Each jurisdiction has its own procedures to review drug submissions filed to their regulatory agency. Generally, in the major markets such as in the United States and the European Union, there are two regulatory steps to go through before a drug is approved to be marketed. These two steps are clinical trial application and marketing authorization. FDA is the regulatory agency which is responsible for safety regulation of the food and drug products in USA. EMA is the regulatory agency and decentralized body which is responsible for safety regulation of the food and drug products in the European Union. In the European Union, however, marketing authorization applications can be approved at both the member state and centralized level at EMA. The average approval time in the USA is 18 months and the European Union 12 months.

It is to be expected, therefore, that after starting directly a phase III study and completing in 2024 the final marketing approval of AADvac1 for both USA and the European Union will be achieved in 2025.

1. CLINICAL PHASE I STUDY "AXON CO 18700" (COMPLETED)

Phase 1 clinical study "Axon CO 18700" (EudraCT 2012-003916-29) consisted of two consecutive parts:

- A 3-month randomised, placebo-controlled, double-blind phase: Patients were randomised in a verum-to-placebo ratio of 4:1 (24 patients were allocated to AADvac1, and 6 to placebo). 3 doses of AADvac1 (or placebo) were administered at 4-week intervals. The double-blind phase was concluded 4 weeks after the 3rd dose;
- A 3-month open label extension phase: Patients received another 3 doses of AADvac1 at 4-week intervals; placebo patients crossed over to AADvac1.

The primary objective of the study was to assess the safety and tolerability of multiple administrations of AADvac1 in patients aged 50-85 years with mild-to-moderate Alzheimer's disease dementia (diagnosed according to the NINCDS-ADRDA criteria) and with MMSE 15-26.

Immunogenicity was assessed as a basic efficacy parameter, being a prerequisite for clinical efficacy.

Clinical efficacy was assessed in an exploratory manner.

In total, 30 patients were enrolled in the study; 28 patients completed the study.

All patients who completed the double-blind part of the study entered the open-label part and have been treated with AADvac1 (placebo patients were switched to AADvac1 treatment). The study is completed and the data have been published (Novak et al., 2017).

Data from this first-in man study confirmed that the vaccine was safe and well tolerated for all parameters assessed. The majority of patients developed a robust immune response to the vaccine and cognition was stable over six months. On the basis of these encouraging results AADvac1 has progressed to the next phase of clinical development in the treatment of Alzheimer's disease and related tauopathies.

2. CLINICAL FOLLOW-UP STUDY "AC-AD-002" (COMPLETED)

Study AC-AD-002 (EudraCT 2013-004499-36) was an 18-month open-label, single arm, multi-centre Phase 1 follow-up study to assess long-term safety and tolerability of AADvac1 in patients with mild to moderate Alzheimer's disease who previously completed study AXON CO 18700, the first-in-man Phase 1 study of AADvac1.

Patients randomised to placebo in the earlier Study AXON CO 18700, who received only 3 doses of AADvac1 open label, received the additional 3 doses of AADvac1 to complete the 6-dose primary vaccination series. All patients received two additional booster vaccinations at 6-month intervals. Patients were followed for up to 72 weeks after the final visit of study AXON CO 18700, thus 96 weeks after receipt of the first treatment with AADvac1.

The primary objective was to assess long-term safety and tolerability of the AADvac1 vaccine in patients aged 50-85 years with mild-to-moderate Alzheimer's disease and the secondary objectives were to assess the immunological, biochemical and clinical efficacy of the treatment. Efficacy was evaluated on the basis of immunological variables, cognitive variables and MRI imaging of the brain.

In total, 26 patients continued in the follow up study (2 patients did not consent to continue) and 20 patients completed the study.

The long-term safety and tolerability of AADvac1 was demonstrated in patients with mild to moderate AD, with no deaths, no related SAEs and no abnormalities in vital signs, ECGs, MRI, physical or neurological examinations that were considered relevant to AADvac1 vaccination.

As expected, antibody titres decreased over time, however antibody persisted in all patients 6 months after the primary vaccination series and 6 months after booster vaccinations (administered at intervals of 6-months). Antibody titres increased significantly after the booster vaccination, with levels comparable to those after the primary vaccination series.

Despite the limitations of the study (small sample size, no placebo control, heterogenous population of mild and moderate AD patients, no CSF biomarker data), positive trends were observed in MRI volumetry and in cognitive assessments, with hippocampal volume loss rates lower than the cited average for AD patients and with only slight decreases in cognitive assessments over the 72-week study period.

AADvac1 displayed a benign safety profile. The evolution of IgG titres over vaccination-free periods warrants a more frequent booster dose regimen. The tendency towards slower atrophy in MRI and less decline in cognitive assessment in patients with high titres is encouraging.

The follow-up study supports the initial findings of the Phase 1 study AXON CO 18700. On the basis of the favourable safety profile and the robust immune responses generated, AXON's AADvac1 vaccine has a very positive risk/benefit balance and Phase 2 has been completed, using the lessons learned from the Phase 1 studies.

3. CLINICAL PHASE II STUDY "AC-AD-003" (COMPLETED)

Phase 2 clinical study "ADAMANT" (EudraCT 2015-000630-30) was a 24-months randomised, placebo-controlled, parallel group, double blind, multi-centre, Phase 2 study to assess safety and efficacy of AADvac1 applied to patients with mild Alzheimer's disease.

The primary objective of the study was to assess the safety and tolerability of multiple administrations of AADvac1 in patients aged 50-85 years with mild Alzheimer's disease dementia (diagnosed according

to the NIA-AA 2011 criteria), evidence of the Alzheimer's disease pathophysiological process in MRI and/or CSF biomarkers, and MMSE 20-26.

Measures of immunogenicity and clinical efficacy constitute the study's secondary endpoints. Cognition and function were assessed by a range of state-of-the art and novel tools, such as the Clinical Dementia Rating scale, the ADCS Activities of Daily Living scale (MCI version), and a Custom Cognitive Battery tailored to the studied population (mild AD).

A range of biomarker assessments were being performed to assess the impact of AADvac1 treatment on AD pathophysiology – MRI volumetry, FDG PET, NfL, CSF biomarkers. Perhaps most importantly, the impact of the strength of the antibody response induced by AADvac1 on disease progression and biomarkers was analysed.

Patient enrolment was concluded in May 2017; a total of 196 patients has been enrolled into the study and randomised in a 3:2 ratio between AADvac1 and placebo.

ADAMANT study completed with encouraging and positive results:

- Successfully meets primary endpoint, confirming exceptional safety profile
- Highly statistically significant impact on neurodegeneration, suggesting disease modifying effect on Alzheimer's Disease
- Compelling trends shown on multiple disease-specific biomarkers and cognitive outcomes, most pronounced among a younger population

For the primary endpoint, the ADAMANT trial showed that AADvac1 has proven to be safe and well tolerated, with no difference in the incidence and nature of adverse events between the treatment and placebo groups. No other safety signals emerged from any other safety or medical assessments. This confirms the overall benign safety profile of AADvac1, demonstrated in prior clinical trials.

AXON's vaccine is an immunotherapy, harnessing the body's immune system to produce specific antibodies. In the Phase II trial, the treatment was shown to be highly effective in inducing a robust immune response, with 98.2% of patients generating antibodies against pathological tau. The finding is consistent with previous observations in the Phase I study and support excellent immunogenicity in this population.

A highly statistically significant impact was seen on neurodegeneration and neuronal loss, as measured in blood by Neurofilament Light Chain ("NfL"). It showed a marked slow-down of the expected increase of NfL in the patients treated with AADvac1, demonstrating a 12.6% change from baseline over two years versus 27.7% for patients on placebo (p value = 0.0039). This indicates that AADvac1 slows the progression of the neurodegenerative process to levels that are more typically seen in healthy individuals.

NfL is a biomarker to track and monitor effects on neurodegeneration in patients with Alzheimer's Disease, Multiple Sclerosis and other neurological disorders.

Compelling trends were observed in the reduction of three separate cerebrospinal fluid ("CSF") Alzheimer's Disease specific biomarkers in treated patients, including two variants of pathological tau (phospho-Tau181 and phospho-Tau217). Despite of a smaller sample size of patients providing required lumbar punctures, the shown effect sizes were large to moderate. This strongly suggests that AADvac1 is successful in slowing the progression of tau pathology.

Positive signals for cognitive endpoints were observed among younger populations in the Phase II trial. These were showed on clinical outcome measure CDR-SB and consistently further across a wide range of additional endpoints including MMSE, ADCS-MCI-ADL, MRI brain volumetry and DTI.

Clinical Dementia Rating – Sum of Boxes, Mini Mental State Examination and Activities of Daily Living are widely accepted clinical outcome measures to asses cognitive and functional decline in Alzheimer's Disease, while Magnetic Resonance Imaging and Diffusion Tensor Imaging are biomarkers that track the level of brain atrophy and damage, which are associated with the progression of the disease.

4. CLINICAL PHASE I STUDY IN NON-FLUENT PRIMARY PROGRESSIVE APHASIA (ONGOING)

Phase 1 study AC-TP-001 (EudraCT 2017-000643-41) is a 24-month randomised parallel group single-blind multi-centre phase 1 pilot study of AADvac1 in patients with non-fluent primary progressive aphasia (nfppA). The study participants will be randomly assigned to two arms with AADvac1 at dosage strength of either 40 µg/0.30 mL or 160 µg/0.30 mL and will be investigated for 24 months. The primary objectives are safety and immunogenicity of AADvac1 in patients with nfPPA, the exploratory objectives address efficacy and immunogenicity of AADvac1, effect of AADvac1 on brain atrophy and biomarkers in blood and CSF.

AXON Neuroscience successfully enrolled 33 patients, randomized 1:1 into two arms to study treatment. The study is performed at 4 centers in Germany. The first patient was administered AADvac1 on 7th August 2017. The recruitment of patients was finalised in Q4 2018.

Part 1 of the study (after 12 months of treatment) is expected to be completed in Q4 2019 and the study is expected to be completed in Q4 2020 – Q1 2021.

5. CLINICAL DEVELOPMENT PLAN OVERVIEW