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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☒	☐ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐ A description of all covariates tested
☒	☐ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☒	☐ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☒	☐ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	*Provide a description of all commercial, open source and custom code used to collect the data in this study, specifying the version used OR state that no software was used.*
Data analysis	*Provide a description of all commercial, open source and custom code used to analyse the data in this study, specifying the version used OR state that no software was used.*

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The described animal studies generally utilized 3-4 animals per group per 3Rs principles.
Data exclusions	No data were excluded.
Replication	The described animal studies were not replicated per 3Rs principles. The average and mean for each group of animals is presented.
Randomization	The animals were randomized based on body weight.
Blinding	The rodent studies were dosed by one group, and the tissues were transferred to another group for analysis. The NHP studies were dosed at CROs, and the tissues were transferred to Alnylam for analysis.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	The following antibodies were used for IHC and are described in the methods: IBA1 1:1600 (#019-19741, Fujifilm Wako, Richmond, VA), GFAP 1:4000 (#Z0334, Agilent-Dako, Santa Clara, CA), CD31 1:75 (#ab23874, Abcam, Waltham, MA), MAP2 1:1000 (#ab5392, Abcam), TTR 1:800 (prealbumin, #SC-8104, Santa Cruz Biotechnology, Dallas, TX), and in-house anti-siRNA rabbit polyclonal antibody ab19151 at 1:12000. The following antibodies were used for ELISA and are described in the methods: sAPPα and sAPPβ (Meso Scale Discovery, K15120E), rabbit anti-human TTR pAb (Dako, A0002), and anti-hTTR pAb (Abcam, ab9015).
Validation	The antibodies were validated utilizing tissues known to lack or express the analyte of interest. Morphological confirmation of expression in a specific cell type within a tissue was used as an additional validation.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Rat RPE-J cells (ATCC, CRL-2240)
Authentication	No authentication
Mycoplasma contamination	Not tested for mycoplasma contamination
Commonly misidentified lines (See ICLAC register)	None

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Mouse (C57BL/6, female, 8-10 weeks), Rat (Sprague Dawley, male, 8-10 weeks), Monkey (Cynomolgus, male and female, 1.5-3 years)
Wild animals	None
Field-collected samples	None
Ethics oversight	All studies were conducted using protocols consistent with local, state and federal regulations, as applicable, and approved by the Institutional Animal Care and Use Committee (IACUC) at Alnylam Pharmaceuticals, Charles River Laboratories (CRL), or LabCorp (formerly Covance, Inc.), as applicable.

Note that full information on the approval of the study protocol must also be provided in the manuscript.