Lu AF82422: Potential first disease-modifying therapy in Multiple System Atrophy

Investor conference call

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Living with migraine

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Multiple System Atrophy (MSA) is a rare, sporadic, rapidly progressing neurodegenerative disease

MSA is clinically characterised by **autonomic failure, cerebellar ataxia** and **parkinsonism** in varying combinations, with an age of onset typically between **55–60** years[1–6]

MSA is an **orphan disease**, with a mean incidence in the US of 0.6:100,000 person-years, increasing with ≥50 years of age to 3:100,000 person-years[2,7]

Prevalence estimates for MSA range from **1.9–4.9 per 100,000 worldwide**, suggesting that environmental, genetic, and epigenetic influences contribute to disease pathogenesis[2,7]

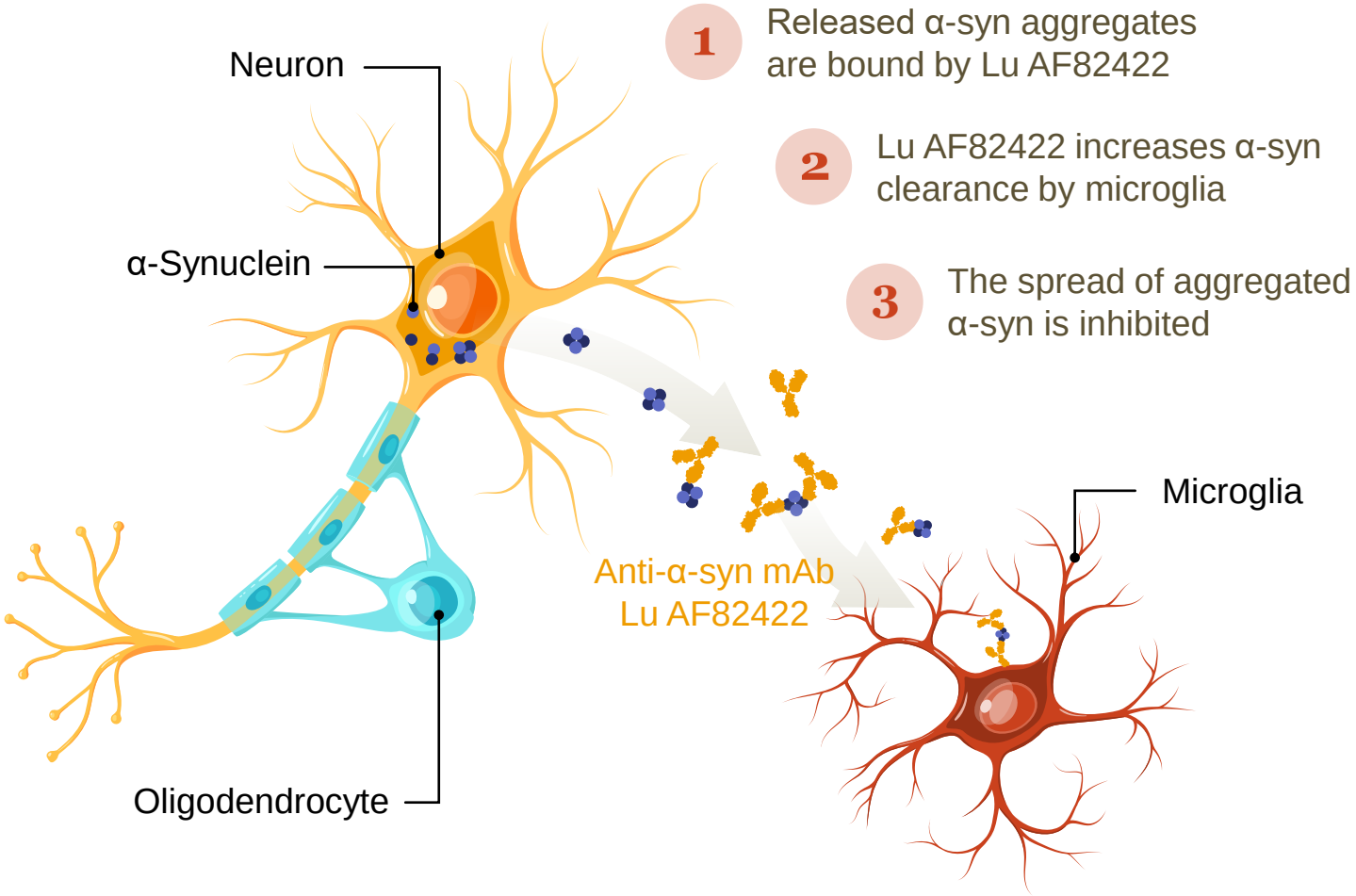
Currently only symptomatic and supportive therapies available

Lu AF82422 has potential to become first therapy capable of delaying disease progression

[1]Gilman S et al. Neurology 2008:1:670–76: [2]Krismer F, Wenning GK. Nat Rev Neurol 2017:13:232–43: [3]Fanciulli A et al. Int Rev Neurobiol 2019:149:137–92: [4]Wenning GK et al. Lancet Neurol 2013:12:264–74: [5]Low PA et al. Lancet Neurol 2015:14:710–19: [6]Palma JA et al. Auton Neurosci 2018:211:15–25: [7]Fanciulli A, Wenning GK. N Eng J Med 2015:372:249–63

Inhibiting the spread to other cells

Lu AF82422 potential first disease-modifying therapy in MSA



1. Released α-syn aggregates are bound by Lu AF82422
2. Lu AF82422 increases α-syn clearance by microglia
3. The spread of aggregated α-syn is inhibited

Lu AF82422 MoA

- Is a human IgG1 mAb that recognizes and binds to all major forms of extracellular α-syn and thereby prevents uptake and inhibit seeding of aggregation
- Has an active Fc region, which may increase immune-mediated clearance of α-syn/mAb complexes through microglia mediated uptake
- Is being developed by Lundbeck under a joint research and licensing agreement between Lundbeck and Genmab A/S

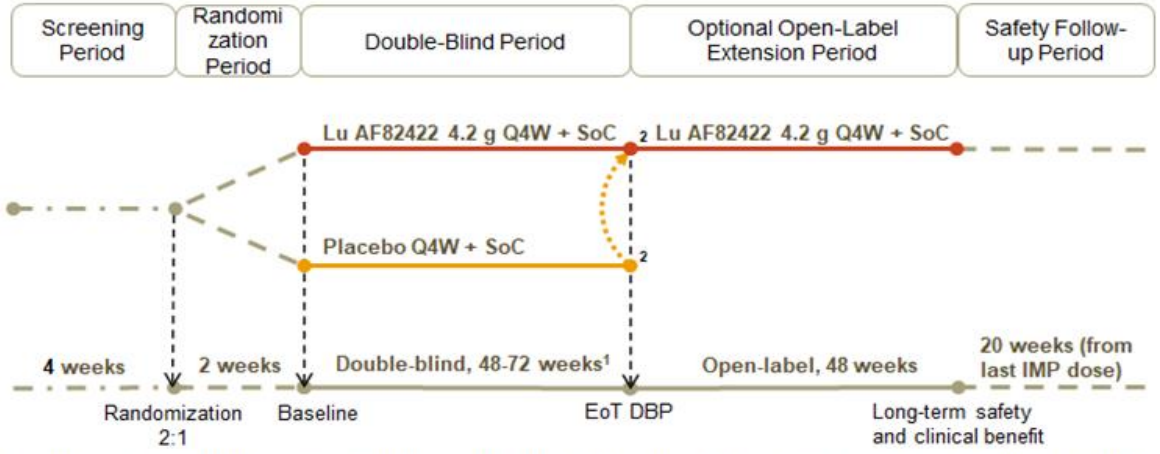
MoA: Mechanism of Action

AMULET was a phase II, randomised, double-blind, placebo-controlled clinical study enrolling 61 patients with MSA

PoC

AMULET trial design

Proof of concept phase II study



- 61 patients from sites in US (18 sites) & Japan (3 sites, maximum 25% of the patients)
- Primary endpoint: Disease progression, as assessed by longitudinal changes from baseline in UMSARS Part I and Part II total score up to EoT

Primary inclusion criteria

- Aged ≥40 and ≤75 years
- Diagnosis of possible or probable MSA (MSA-P or MSA-C)
- <5 years from time of onset of motor symptoms
- Anticipated survival of ≥3 years
- UMSARS Part I score <17*
- MoCA score ≥22
- Knowledgeable and reliable caregiver

Primary exclusion criteria

- ≥2 relatives with MSA
- Past anti-α-syn treatment
- Advanced disease as assessed on UMSARS

*Omitting item 11 on sexual function. †Patients are allowed stable treatment for managing their symptoms of MSA during the study. BL: Baseline. DBP: Double-blind period. EoT: End of treatment. MoCA: Montreal Cognitive Assessment. R: Randomisation. SCR: Screening. SFU: Safety follow-up. SoC: Standard of care. UMSARS: Unified MSA Rating Scale. Q4W: Once every 4 weeks. Study 18331A

AMULET explored a wide range of **secondary endpoints** to better understand the potential of Lu AF82422

Category	Secondary endpoints		
Disease progression	UMSARS Part I, mUMSARS Part I and UMSARS Part II scores*	UMSARS TS, UMSARS Part I, mUMSARS and UMSARS Part II scores†	
Function	SE-ADL score†		
Global impression	CGI-S score†	PGI-S score†	OGI-S score†
Autonomic symptoms	COMPASS Select Change score†	Heart rate, blood pressure, and orthostatic symptoms, as assessed in UMSARS Part III†	
Global disability	UMSARS Part IV score†		
Disease milestones	Speech, swallowing, falls and walking, as assessed by the UMSARS Part I item scores†	Frequency, cause and consequence of falls, as assessed by the fall diary periods†	
Health-related quality of life	EQ-5D-5L score†		
MRI biomarkers	Brain volume in brain ROIs by vMRI†	Tissue integrity in ROIs by DTI MRI†	
Biofluid biomarkers	NfL blood concentrations†		
Pharmacokinetics	Lu AF82422 plasma concentration during treatment and safety follow-up	Lu AF82422 CSF concentrations and the CSF/plasma concentration ratios at Week 48	

*Change from baseline to end of treatment. †Change from baseline to Week 48. CGI-S: Clinical Global Impression – Severity of Illness. COMPASS: Composite Autonomic Symptom Score. CSF: Cerebrospinal fluid. DTI: Diffusion-tensor imaging. EQ 5D 5L: EuroQol 5-dimension 5-level. MRI: Magnetic resonance imaging. mUMSARS: Modified UMSARS. NfL: Neurofilament light chain. OGI-S, Observer-reported Global Impression – Severity of Illness. PGI-S: Patient Global Impression – Severity of Illness. ROI: Regions of interest. SE-ADL: Schwab and England Activities of Daily Living. TS: Total score. UMSARS: Unified MSA Rating Scale. vMRI: Volumetric MRI. Study 18331A

AMULET explored a wide range of **exploratory endpoints** to better understand the potential of Lu AF82422

Category	Exploratory endpoints		
Disease progression	aUMSARS*		
Disease milestones	Time to wheelchair use	Frequency of falls, as assessed by PAMSys device (subset)†	Gait parameters, as assessed by FeetMe device (subset)†
MRI biomarkers	Cerebral blood flow in ROI by ASL MRI†	vMRI, DTI and ASL MRI measures*	
Biofluid biomarkers	t-tau and NfL CFS concentrations†	NfL blood concentrations*	
α-synuclein targeting	Plasma concentrations of 'free' and 'total' α-synuclein during treatment and safety follow-up	Concentrations of 'free' and 'total' α-synuclein†	
CSF biomarkers	Pathological species of α-synuclein†		
Relationship	Relationship between UMSARS TS, Part I and Part II scores, brain volume and tissue integrity in brain ROIs as measured by MRI, and NfL concentrations†		
Clinical scales	UMSARS Part I items 1, 2, 7 and 8, Part III and Part IV, and SE-ADL, CGI-S, PGI-S, OGI-S, COMPASS Select Change and EQ-5D-5L*		
Patient experience	Describe patient experience data, as assessed by the Screening and Exit interviews		

*Change from baseline to end of treatment. †Change from baseline to Week 48. ASL: Arterial spin labelling. aUMSARS: Abbreviated UMSARS. CGI-S: Clinical Global Impression – Severity of Illness. COMPASS: Composite Autonomic Symptom Score. CSF: Cerebrospinal fluid. DTI: Diffusion-tensor imaging. EQ 5D 5L: EuroQol 5-dimension 5-level. MRI: Magnetic resonance imaging. NfL: Neurofilament light chain. OGI-S: Observer-reported Global Impression – Severity of Illness. PGI-S: Patient Global Impression – Severity of Illness. ROI: Regions of interest. TS: Total score. t-tau: Total tau. UMSARS: Unified MSA Rating Scale. vMRI: volumetric MRI. Study 18331A

Baseline characteristics of AMULET trial by MSA sub-type

		MSA-C N=41	MSA-P N=20	Overall N=61
Age (years)		60.9 (7.7)	60.7 (7.8)	60.8 (7.7)
Sex, n (%)	Female	19 (46%)	10 (50%)	29 (47.5%)
	Male	22 (54%)	10 (50%)	32 (52.5%)
Race, n (%)	White	28 (68%)	13 (65%)	41 (67%)
	Asian[1]	11 (27%)	6 (30%)	17 (28%)
	Black	1 (2%)	1 (5%)	2 (3%)
	Other	1 (2%)	-	1 (2%)
Diagnostic certainty, n (%)	Probable	25 (61%)	14 (70%)	39 (37%)
	Possible	16 (29%)	6 (30%)	22 (36%)
Time since diagnosis (years)		1.5 (1.1)	1.2 (0.9)	1.4 (1.1)
Time since onset of symptoms		3.5 (1.2)	3.1 (1.2)	3.3 (1.2)
Plasma NFL (pg/mL)		28.4 (8.5)	36.6 (18.3)	31.1 (13.0)

	MSA-C N=41	MSA-P N=20	Overall N=61
Part I (Functional disability)	15.9 (3.6)	18.0 (4.0)	16.6 (3.8)
Part II (Motor impairment)	17.4 (5.4)	22.1 (5.7)	19.0 (5.9)
UMSARS total score (Parts I+II)	33.3 (7.5)	40.1 (9.1)	35.5 (8.6)
Modified UMSARS[2]	18.4 (3.0)	20.0 (3.2)	18.9 (3.1)
Part III, Orthostatic Symptoms n (%)	14 (34.1%)	8 (40.0%)	22 (36.1%)

Baseline characteristics are **consistent with a population of patients with MSA who are still relatively early in their disease course**, and who might be good candidates to assess the slowing of clinical progression with a therapy preventing α-synuclein accumulation

W. Singer, et al., Baseline characteristics for patients with multiple system atrophy entering a randomized, controlled study of the anti-α-synuclein monoclonal antibody Lu AF82422 [abstract]. Mov Disord. 2023; 38 (suppl 1). [1]Japanese. [2]Part I responses of 0 and 1 are collapsed to one category. Higher scores on the UMSARS indicate greater disability. UMSARS: Unified Multiple System Atrophy Rating Scale

Lundbeck announces supportive phase II results with Lu AF82422 in the treatment of MSA from the AMULET trial

Signals of efficacy were observed across clinical and biomarker endpoints in a small exploratory proof-of-concept trial of 61 MSA patients (40 on Lu AF82422 versus 21 on placebo)

Although the AMULET trial did not show statistical significance on its primary endpoint in slowing the rate of progression of MSA as measured by UMSARS Total Score, a trend of a slowing MSA progression was observed in the group exposed to Lu AF82422

Lu AF82422 was generally well tolerated

UMSARS: Unified Multiple System Atrophy Rating Scale. Clinicaltrials.gov ID: NCT05104476

Key drivers of Lu AF82422 success

1. First-in-class antibody with superior technical profile which binds all major forms of α-synuclein and prevents aggregation
2. Clinical Proof of Mechanism achieved and well tolerated in healthy volunteers and PD patients
3. Furthest in development for MSA where currently no approved treatment exists

Q&A

Appendix

Currently no approved treatment for MSA

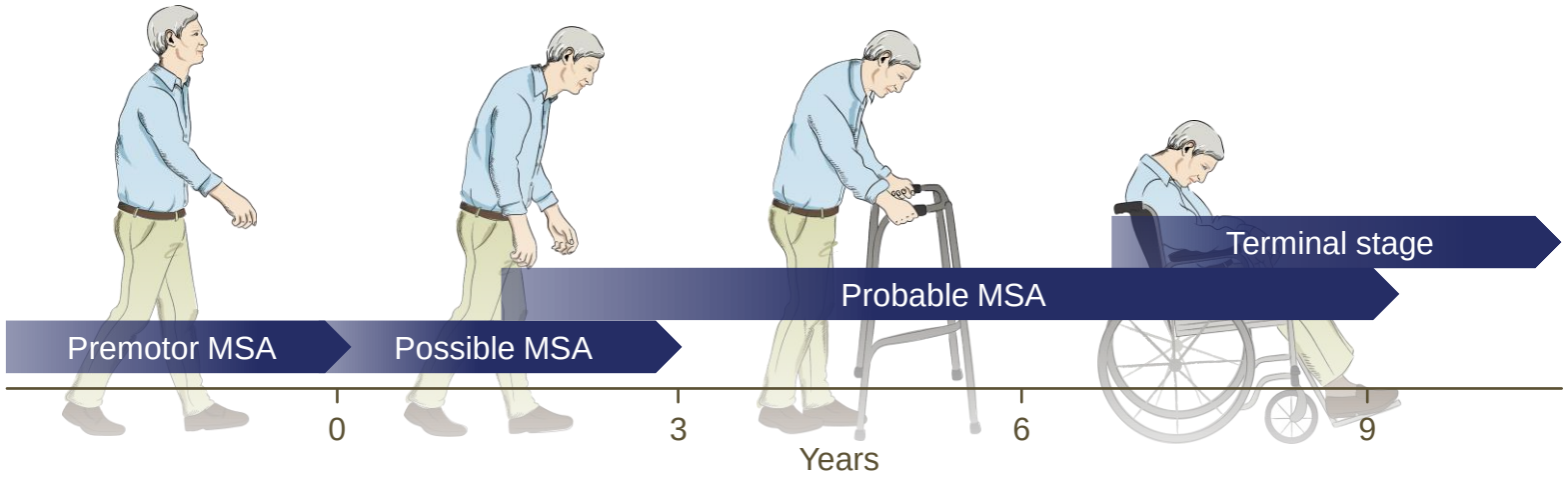
A rapidly progressing and fatal disease

Symptoms

Common symptoms include:

- Slowness of movement, tremor, or stiffness
- Clumsiness or lack of coordination
- Croaky, quivering voice
- Fainting or lightheadedness
- Bladder control problems

The clinical course



50% of patients require walking aids within 3 years of motor symptom onset[2]

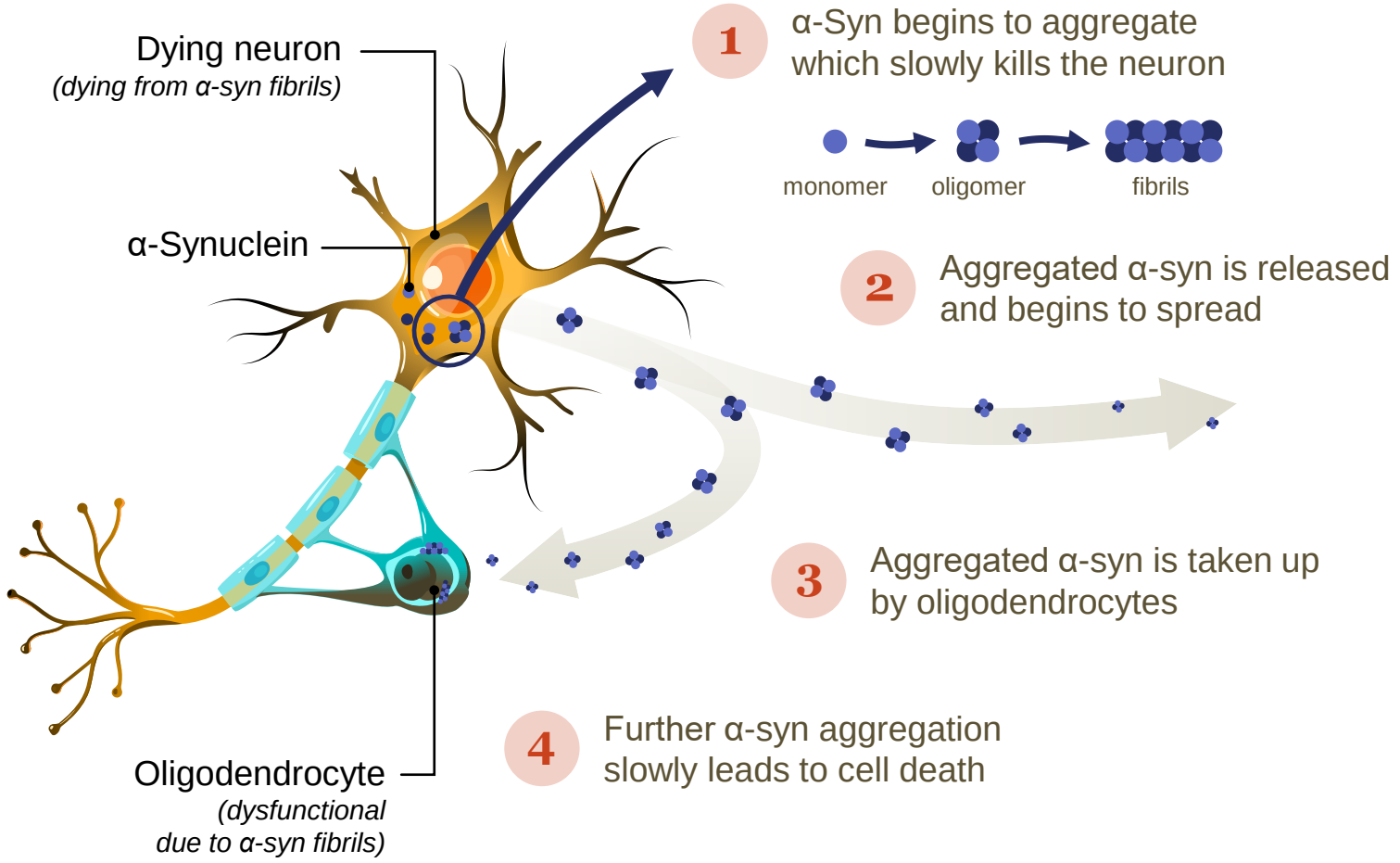
60% of patients require a wheelchair after 5 years and the median time before a patient is bedridden is typically 6–8 years[2]

Mortality usually due to bronchopneumonia, urosepsis, or sudden death[2,3]

1. Krismer F, Wenning GK. Nat Rev Neurol 2017;13:232–43; 2. Fanciulli A, Wenning GK. N Eng J Med 2015;372:249–63; 3. Jellinger KA. J Alzheimers Dis 2018;62:1141–79.

α-Synuclein aggregation kills cells

Spreading of aggregated α-synuclein leads to further neuronal death

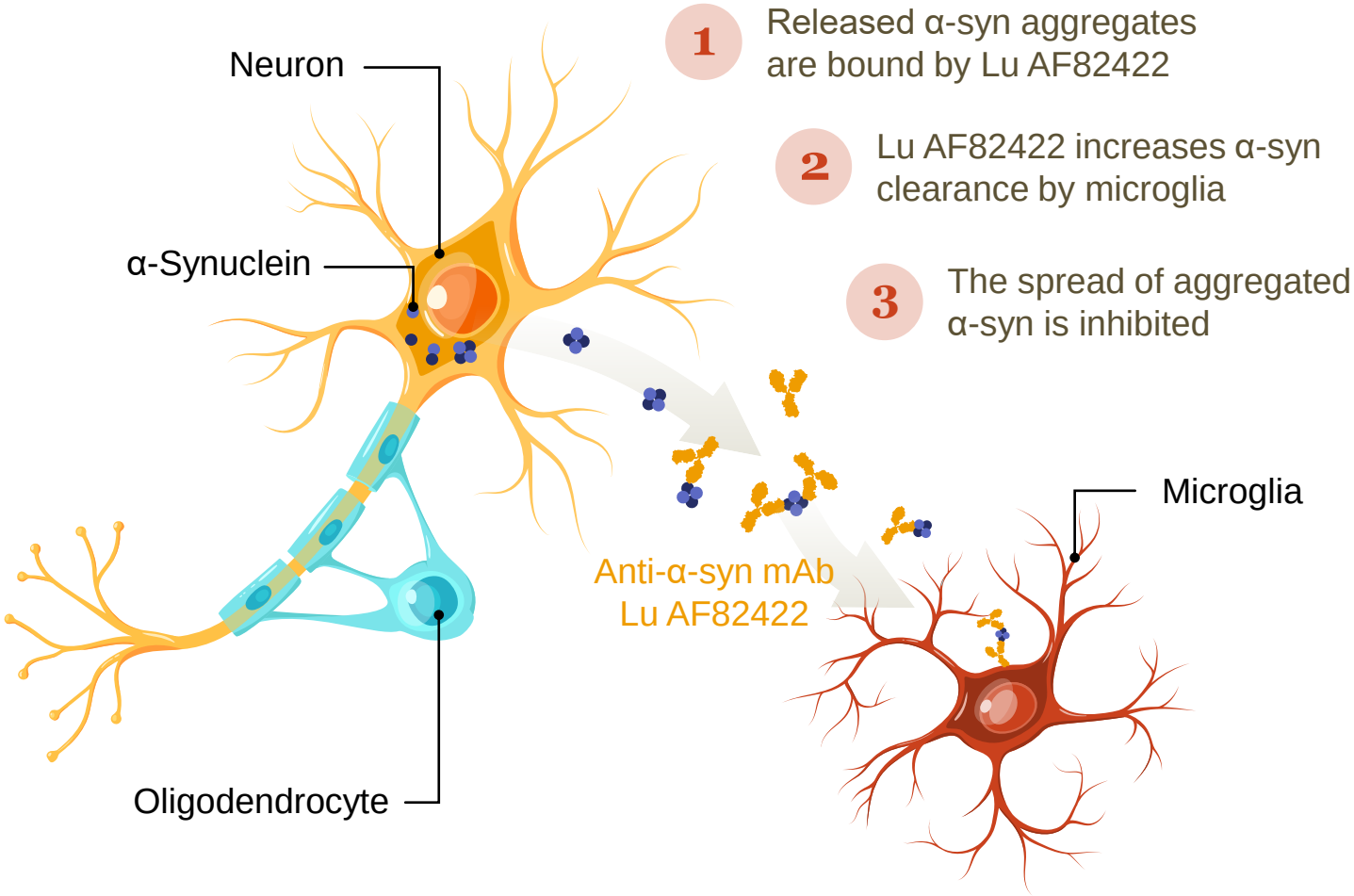


Targeting α-synuclein

- Alpha-synuclein (α-syn) is a neuronal protein involved in the regulation of neurotransmitter release, synaptic function, plasticity, and several other cellular processes
- Under pathological conditions, α-syn accumulates and forms insoluble aggregates leading to cell death.
- The insoluble aggregates constitute the main feature of a group of neuro-degenerative disorders referred to as α-synucleinopathies, which include MSA

Inhibiting the spread to other cells

Lu AF82422 potential first disease-modifying therapy in MSA



Lu AF82422

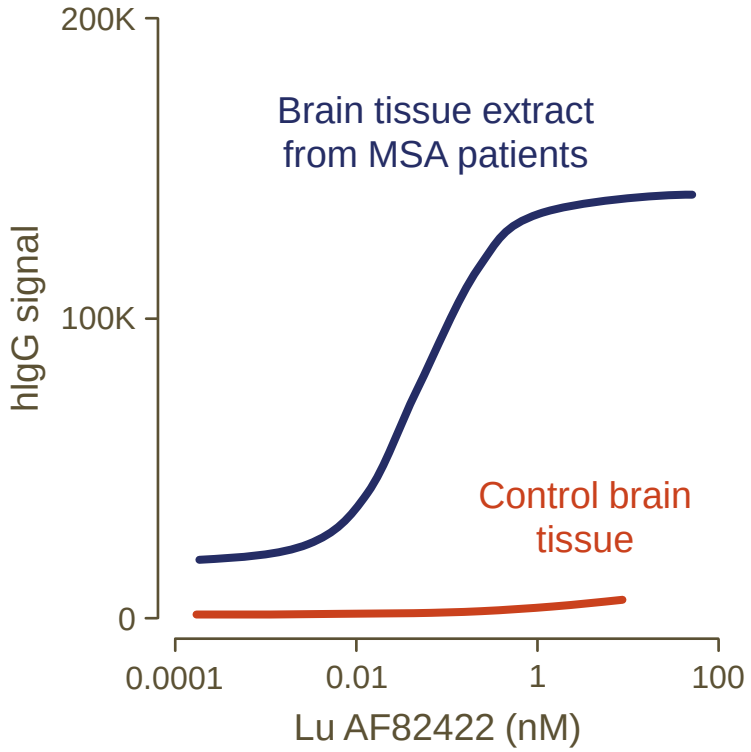
- Lu AF82422 is a human IgG1 mAb that recognizes and binds to all major forms of extracellular α-syn and thereby prevents uptake and inhibit seeding of aggregation
- Lu AF82422 has an active Fc region, which may increase immune-mediated clearance of α-syn/mAb complexes through microglia mediated uptake
- Lu AF82422 is being developed by Lundbeck under a joint research and licensing agreement between Lundbeck and Genmab A/S

Clear pharmacological effect

When tested in tissue from MSA patients

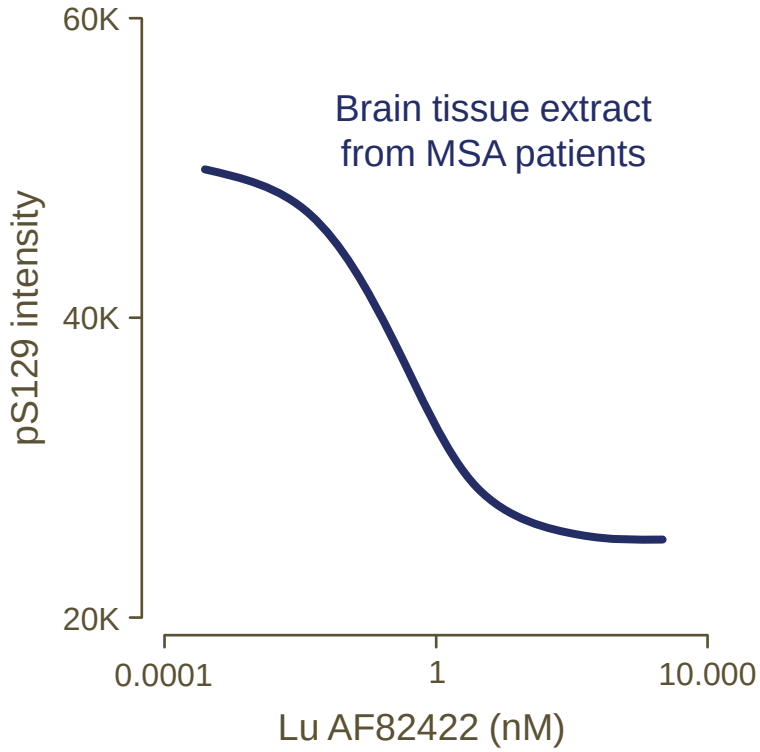
Lu AF82422 binds MSA fibrils

EC_{50} measured as 0.09 nM



Lu AF82422 inhibits seeding

Measured as pS129 fluorescent intensity per cell



Lu AF82422

- Lu AF82422 is a human IgG1 mAb in development as a disease-modifying therapy in MSA
- Lu AF82422 binds to aggregated α-syn isolated from brain tissue in patients with MSA, and inhibits seeding of α-syn by the same brain tissue extract

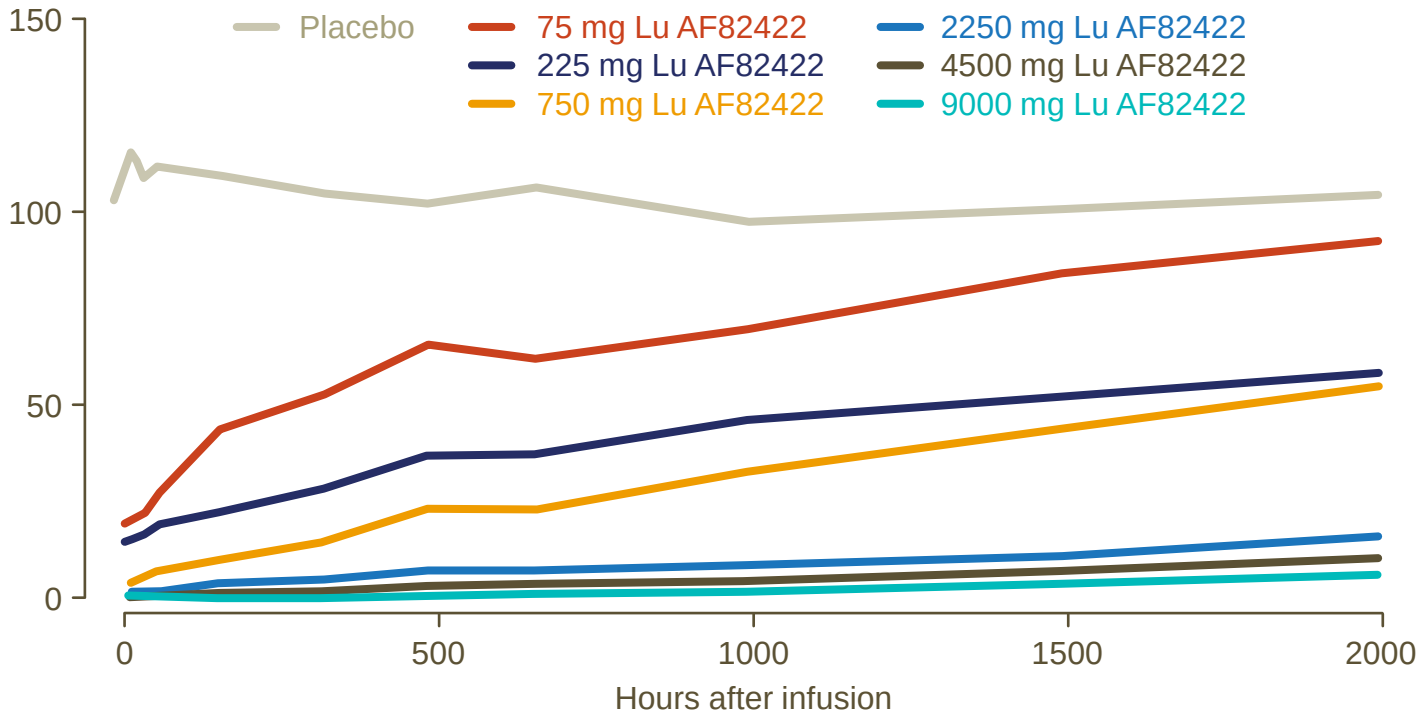
P. Kallunki et al., Mov Disord. 2022; 37,suppl 1

Clinical proof of mechanism

Achieved in healthy volunteers

Lu AF82422 showed reduction of free α-synuclein in plasma in healthy volunteers

Percent free/total α-synuclein ratio



Study design

- First in human single ascending dose (SAD) study done in healthy volunteers and PD patients:
  1. A relevant target population with alpha-synucleinopathy
  2. PD patients are more accessible
  3. Potential expansion of indication
- Randomized, double-blind, sequential group, placebo-controlled study with 58 healthy volunteers and 15 PD patients

Safety

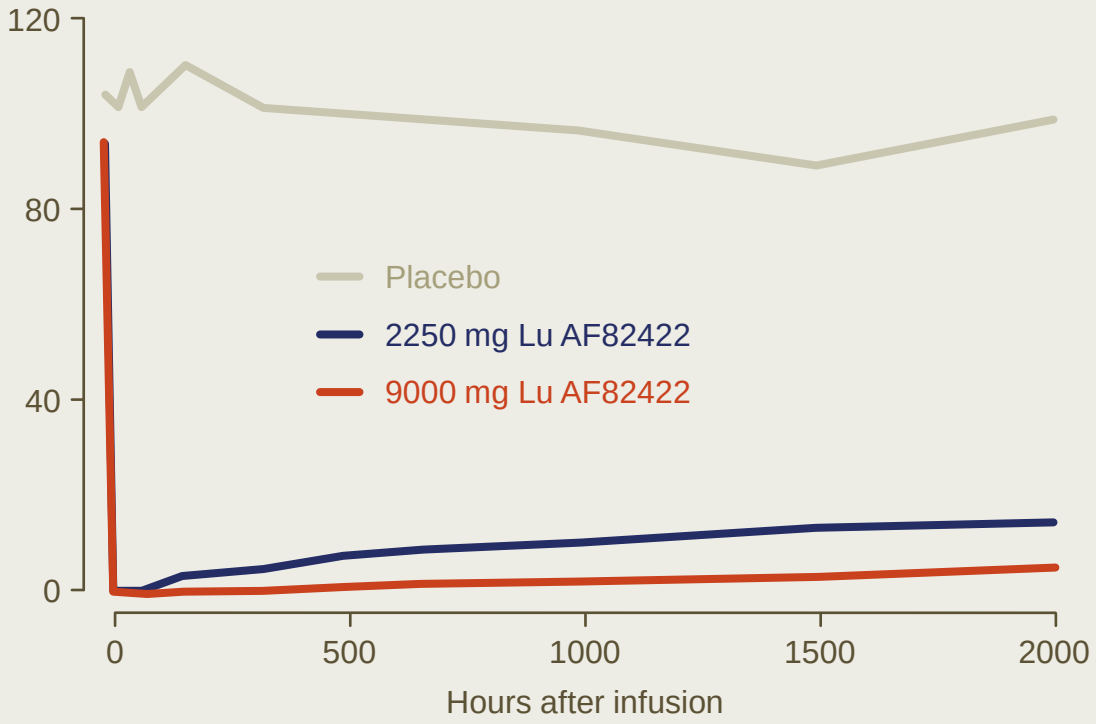
- No safety concerns identified and no apparent difference between PD and healthy controls

17 L. Buur et al., [abstract] Mov Disord. 2022; 37 (suppl 1)

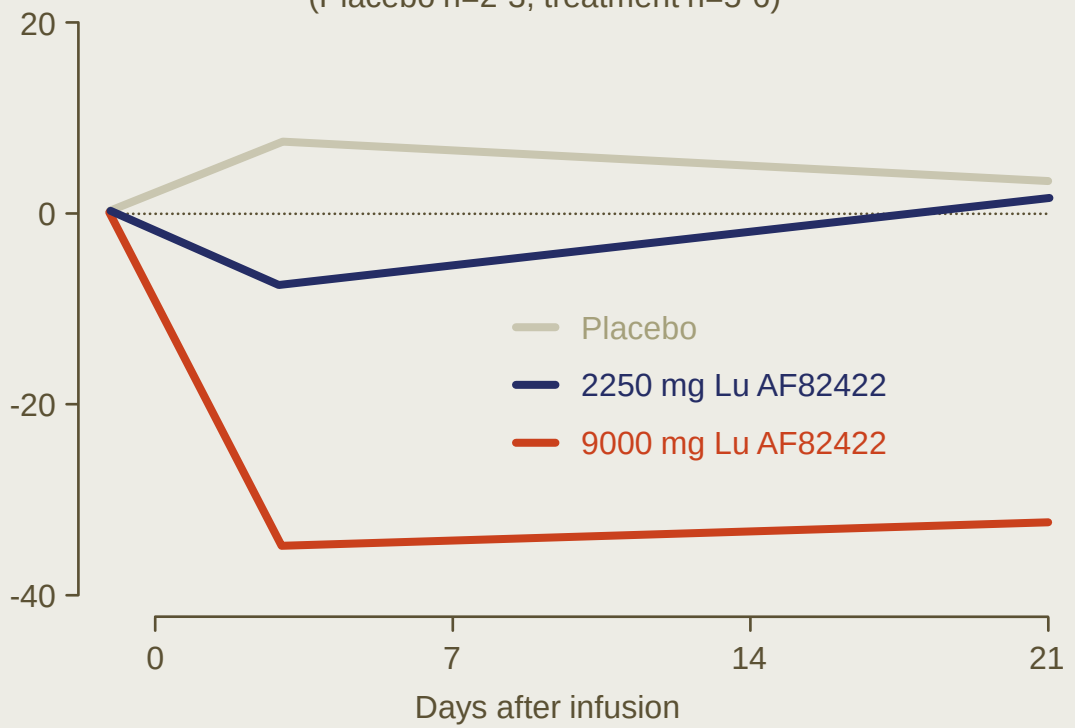
Clinical proof of mechanism

Achieved in Parkinson's patients

Lu AF82422 showed reduction of free α-synuclein in plasma in Parkinson's patients



Lu AF82422 showed reduction in free α-synuclein in CSF from Parkinson's patients



18 L. Buur et al., [abstract] Mov Disord. 2022; 37 (suppl 1)

Potential to be the first disease-modifying MSA treatment

First-in-class capable of delaying disease progression

Potential treatment benefits in MSA

Address underlying pathophysiology
Current treatment is symptomatic or supportive and associated with limited benefits

Meaningful reduction in the rate of clinical deterioration

Delay time to loss of function
Loss of ambulation, speech, etc.

Most advanced therapy currently in clinical development for MSA

Anti-α-syn mAb Lu AF82422

Disease-modifying potential

Potential impact beyond motor symptoms

Improve quality of life

Favorable safety profile
Well tolerated in phase I (healthy volunteers and PD patients) and phase II (MSA patients)

First-in-class potential to slow disease

Slowing disease progression in patients with MSA

Reasons to believe	TAK-341	ASO/ AAV	ATH-434	α-Syn	Patient benefit
Phase II readout before 2025	–	–	–	✓	Potential first to market
Current stage beyond phase I	✓	–	–	✓	Potential first to market
Route of administration	✓	–	✓	✓	Greater patient comfort
Preclinical evidence of binding to toxic species	✓	–	–	✓	Potential to slow clinical disease progression
Preclinical evidence of inhibition of seeding-induced pathology propagation	✓	?	–	✓	Potential to slow clinical disease progression

20 TAK-341: A monoclonal antibody; ASO: Antisense oligonucleotides; AAV: Adeno associated virus; ATH-434: A small molecule drug.

Advantages of a disease modification as first PoC indication

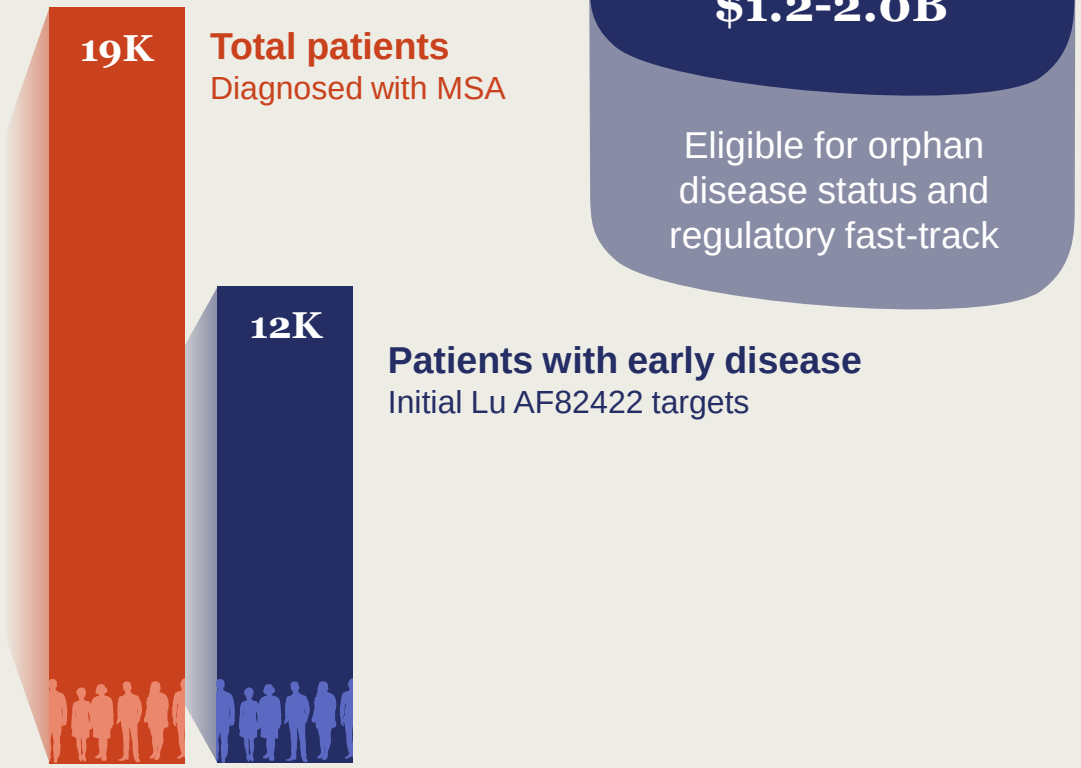
- High unmet medical needs
- No treatment options available
- Regulatory path established

Orphan pricing with significant potential to expand

With the potential to expand to other α-synuclein related diseases such as PD and DLB

US market

Patient data from 2022



Total patients
Diagnosed with MSA

Patients with early disease
Initial Lu AF82422 targets

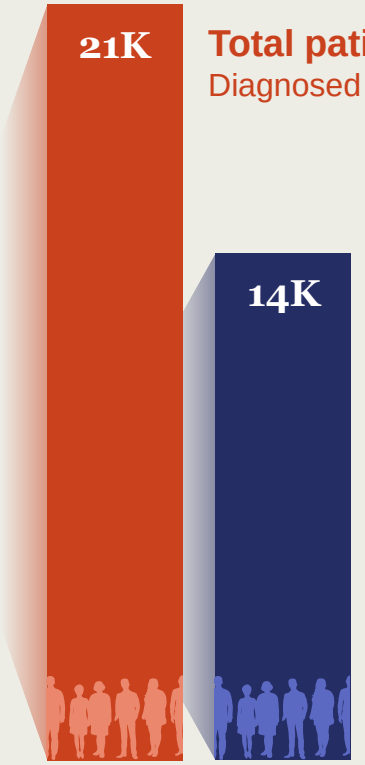
Estimated total market size in 2031

$1.2-2.0B

Eligible for orphan disease status and regulatory fast-track

EU5+JP market

Patient data from 2022



Total patients
Diagnosed with MSA

Patients with early disease
Initial Lu AF82422 targets

Estimated total market size in 2031

$0.3-1.0B

Orphan status and Sakigaki granted and regulatory fast-track potential

Source: Trinity and internal estimates; PD: Parkinso's Disease; DLB: Dementia with Lewy Bodies