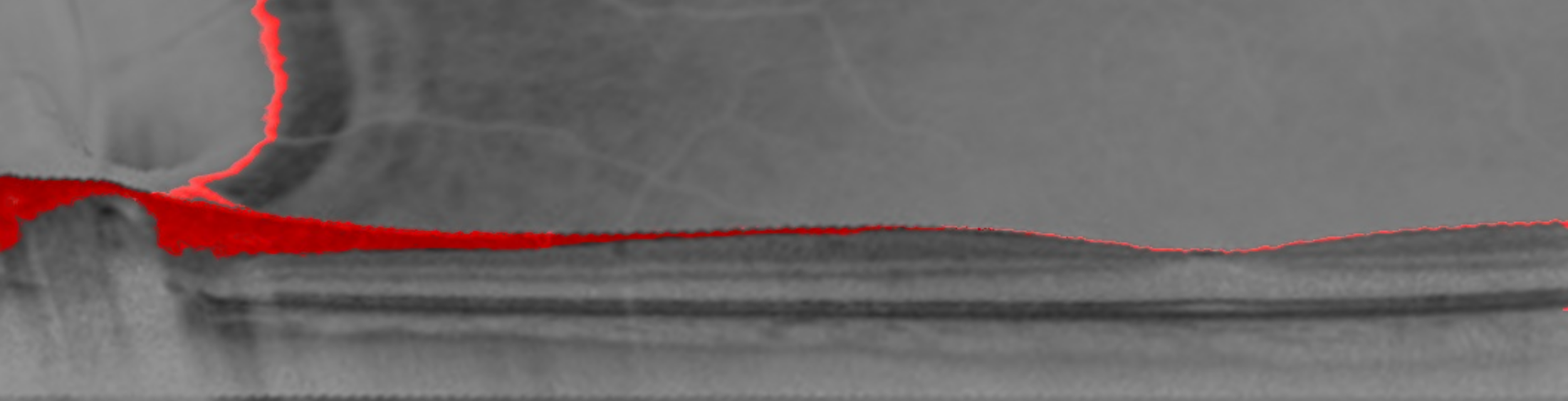


# RemyelINatiON

Sat 16-SEP-2023, 18:30-18:50

axel petzold

Expertisecentrum Neuro-ophthalmology Amsterdam UMC

UCL

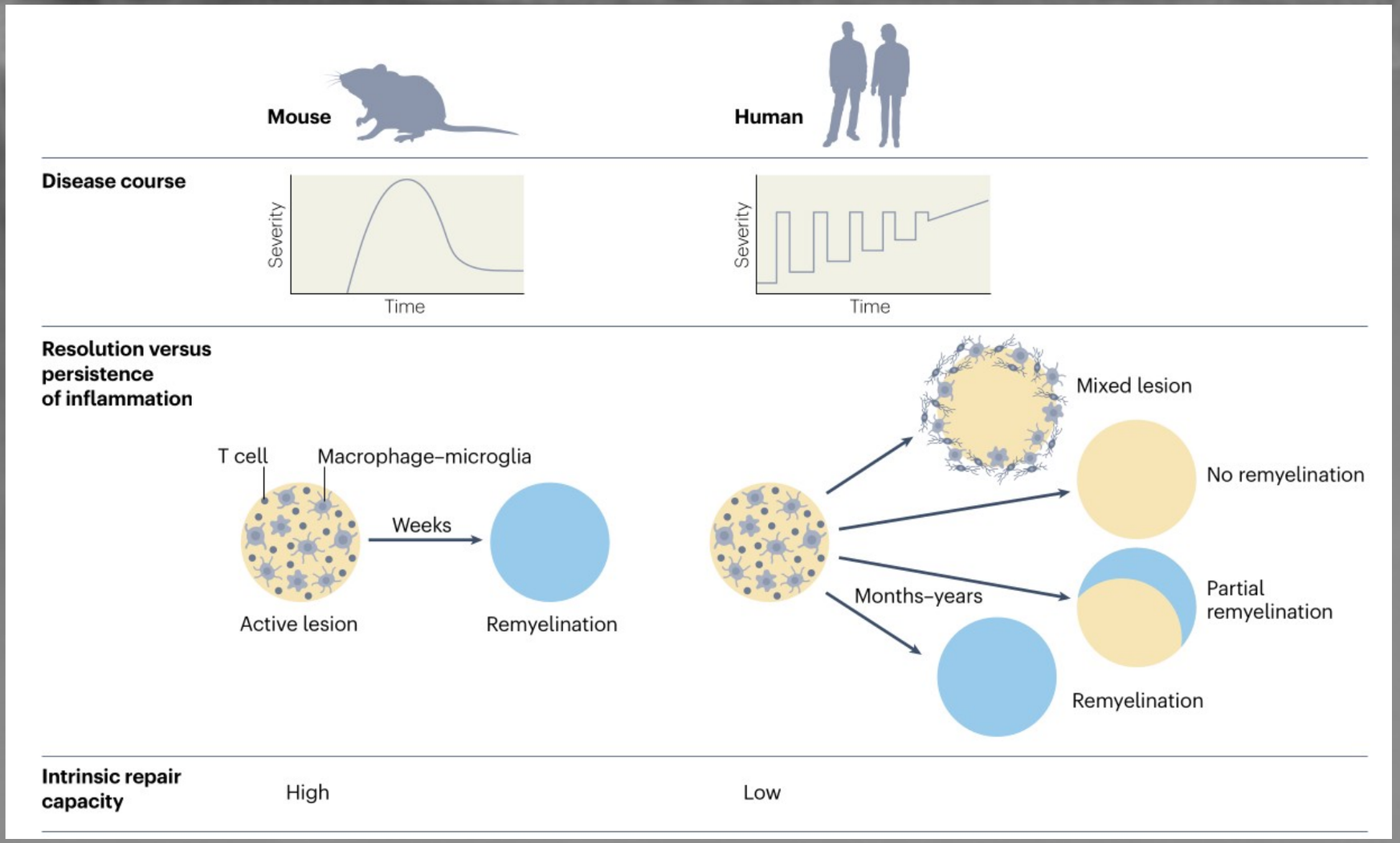
# Disclosures

NIHR UK, UCSF
Stichting MS Research NL
Novartis, Heidelberg Academy

# To be covered

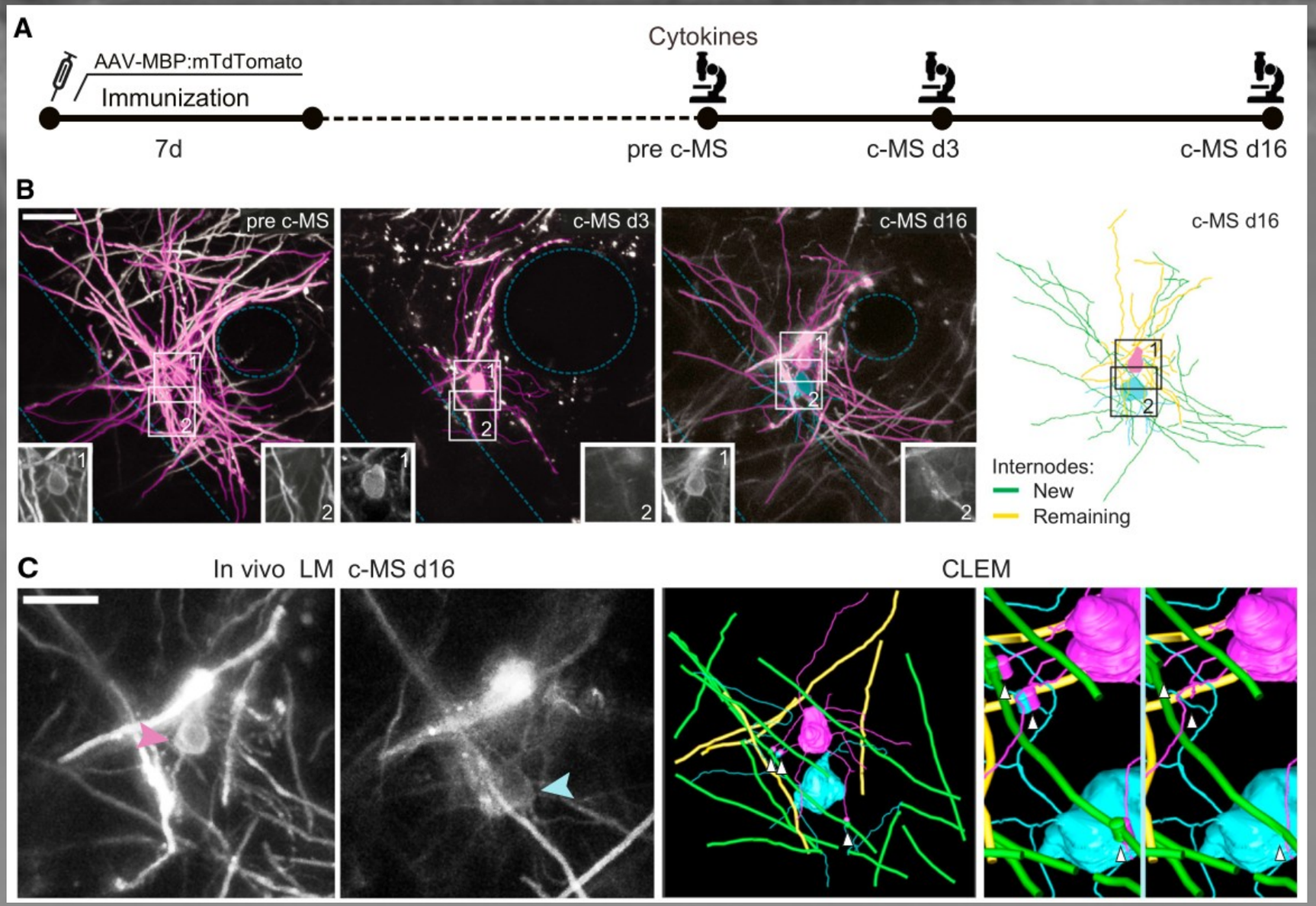
- Background on remyelination
- The key trial in humans
- Novel outcomes
- Novel trials
- Summary

# Remyelination in mice and men



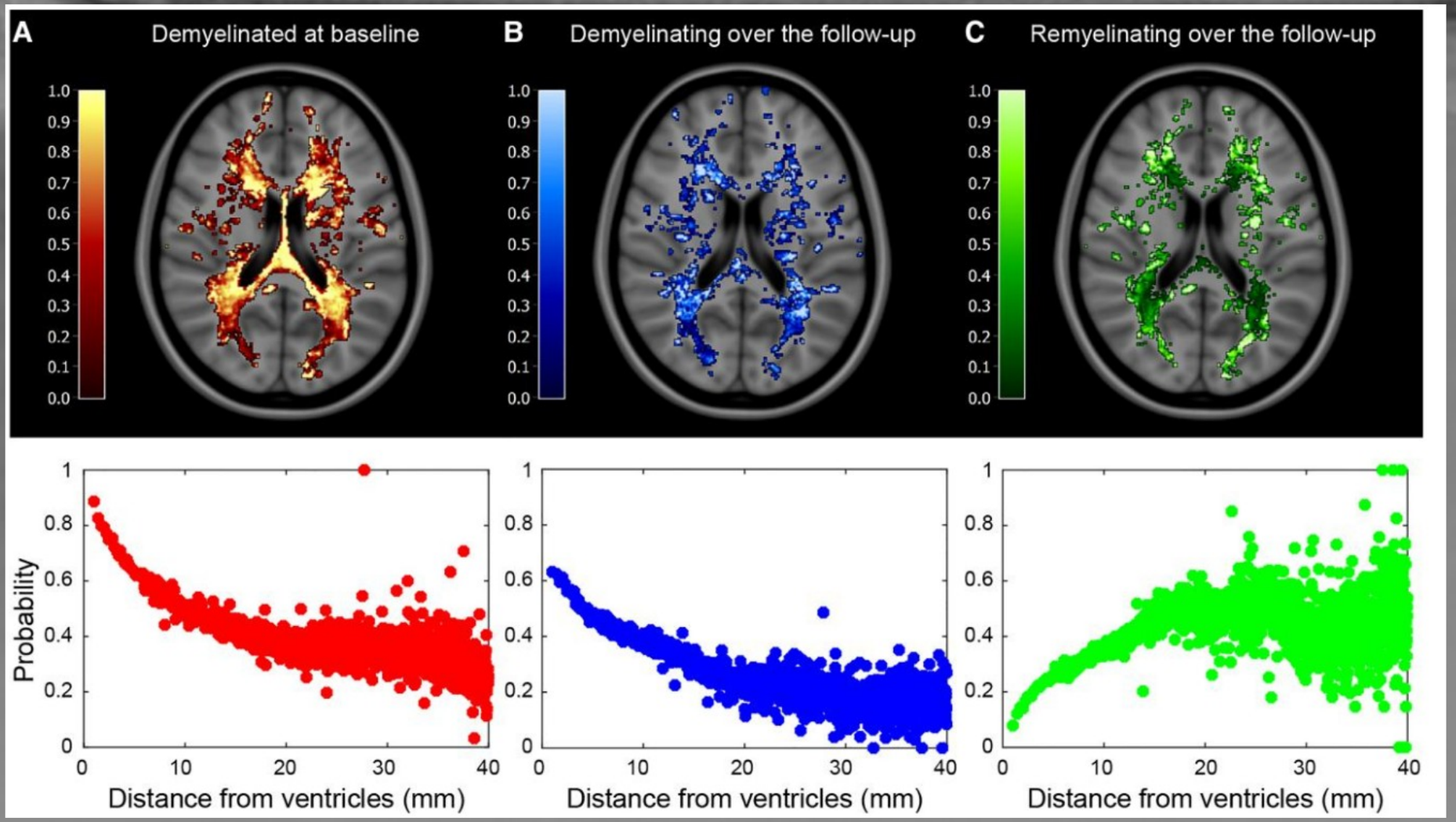

Klotz, L *et al* Nat Rev Neurol 2023

# In mice: remyelination success




Mezydlo, A *et al* Neuron 2023

# In men: remyelination failure




Tonietto, M *et al* Brain 2023

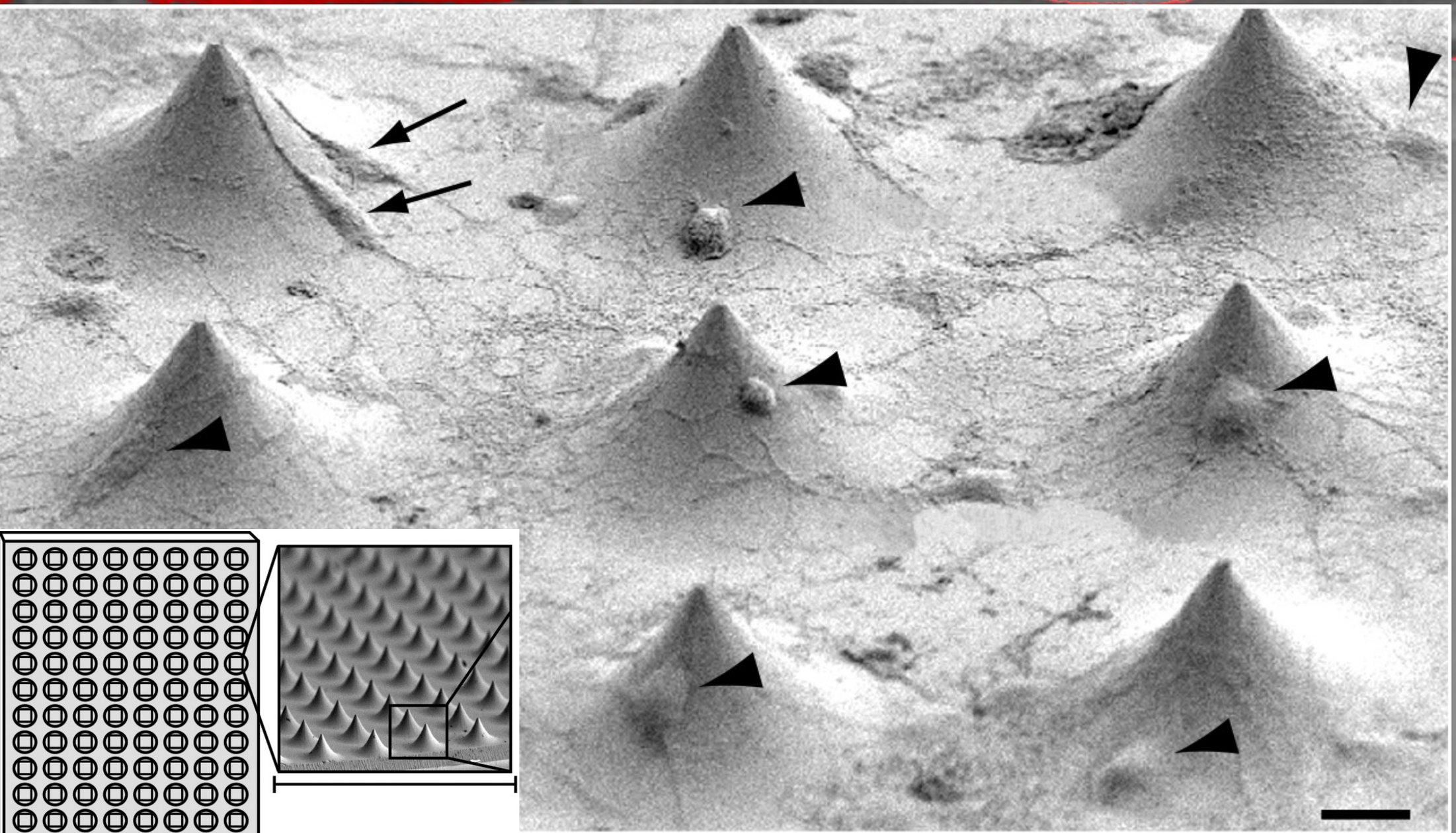
# Remyelination strategies

- Repurposing of safe drugs
- Novel compounds
- Stem cells
- Genetic

# To be covered

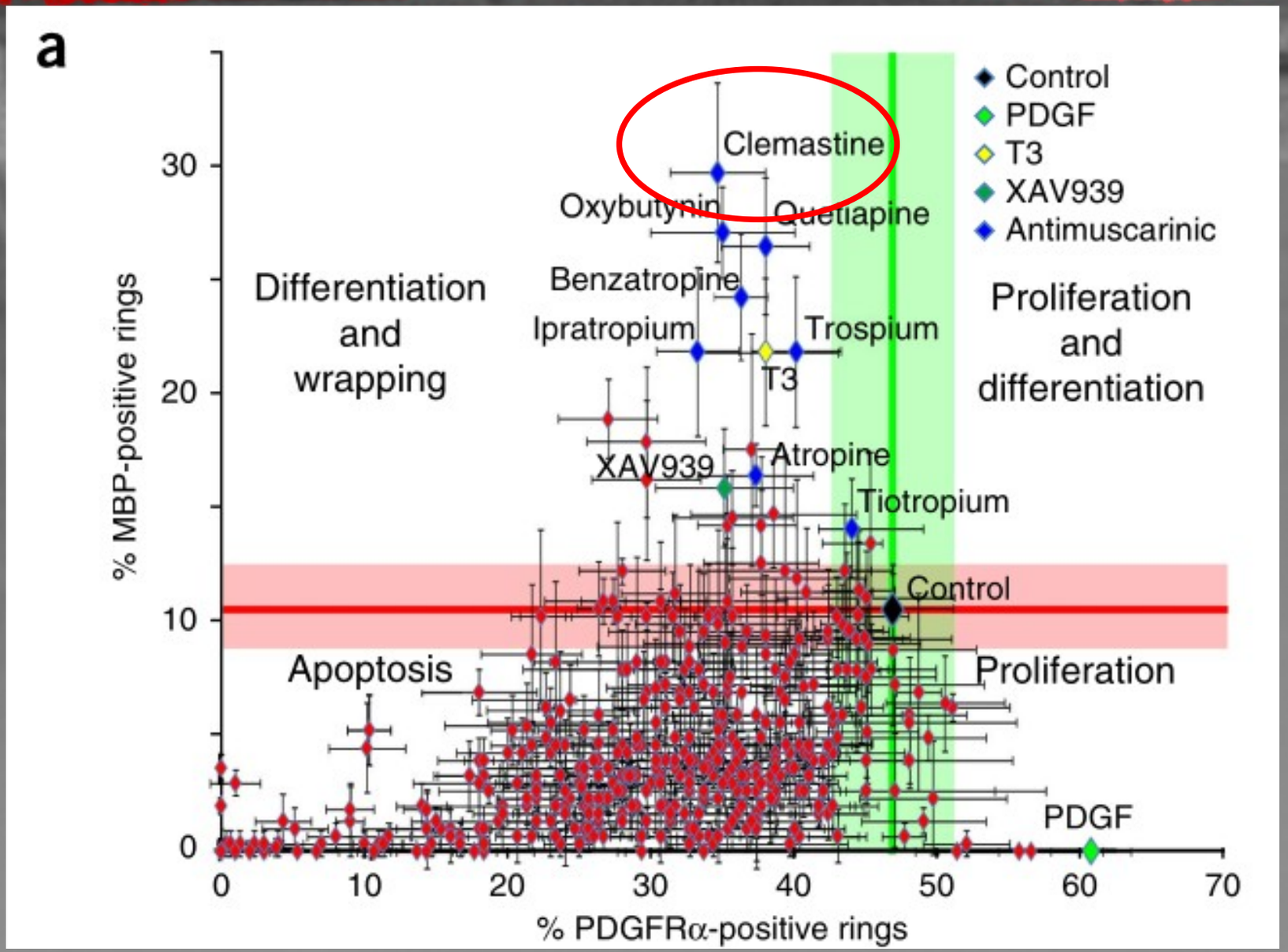
- Background on remyelination
- The key trial in humans
- Novel outcomes
- Novel trials
- Summary

# Preparing the stage



Mei, F *et al* Nat Med 2014

# Choosing the drug




Mei, F *et al* Nat Med 2014

# Make it a safe choice

**Clemastine fumarate:**

- Hay-fever tablet
- > 700,000,000 tablets (1979 to 1992, FDA data)
- 1.4/100,000 AE (mainly fatigue)

# Key trial

## Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomised, controlled, double-blind, crossover trial

*Ari J Green, Jeffrey M Gelfand, Bruce A Cree, Carolyn Bevan, W John Boscardin, Feng Mei, Justin Inman, Sam Arnow, Michael Devereux, Aya Abounasr, Hiroko Nobuta, Alyssa Zhu, Matt Friessen, Roy Gerona, Hans Christian von Büdingen, Roland G Henry, Stephen L Hauser, Jonah R Chan*

### Summary

**Background** Multiple sclerosis is a degenerative inflammatory disease of the CNS characterised by immune-mediated destruction of myelin and progressive neuroaxonal loss. Myelin in the CNS is a specialised extension of the oligodendrocyte plasma membrane and clemastine fumarate can stimulate differentiation of oligodendrocyte precursor cells in vitro, in animal models, and in human cells. We aimed to analyse the efficacy and safety of clemastine fumarate as a treatment for patients with multiple sclerosis.

**Methods** We did this single-centre, 150-day, double-blind, randomised, placebo-controlled, crossover trial (ReBUILD) in patients with relapsing multiple sclerosis with chronic demyelinating optic neuropathy on stable immunomodulatory therapy. Patients who fulfilled international panel criteria for diagnosis with disease duration of less than 15 years were eligible. Patients were randomly assigned (1:1) via block randomisation using a random number generator to

*Lancet* 2017; 390: 2481–89

Published Online
October 10, 2017
http://dx.doi.org/10.1016/S0140-6736(17)32346-2

See Comment page 2421

Department of Neurology
(A J Green MD, J M Gelfand MD, B A Cree MD, C Bevan MD, F Mei PhD, J Inman BS, S Arnow BS, M Devereux BS,

# Outcome

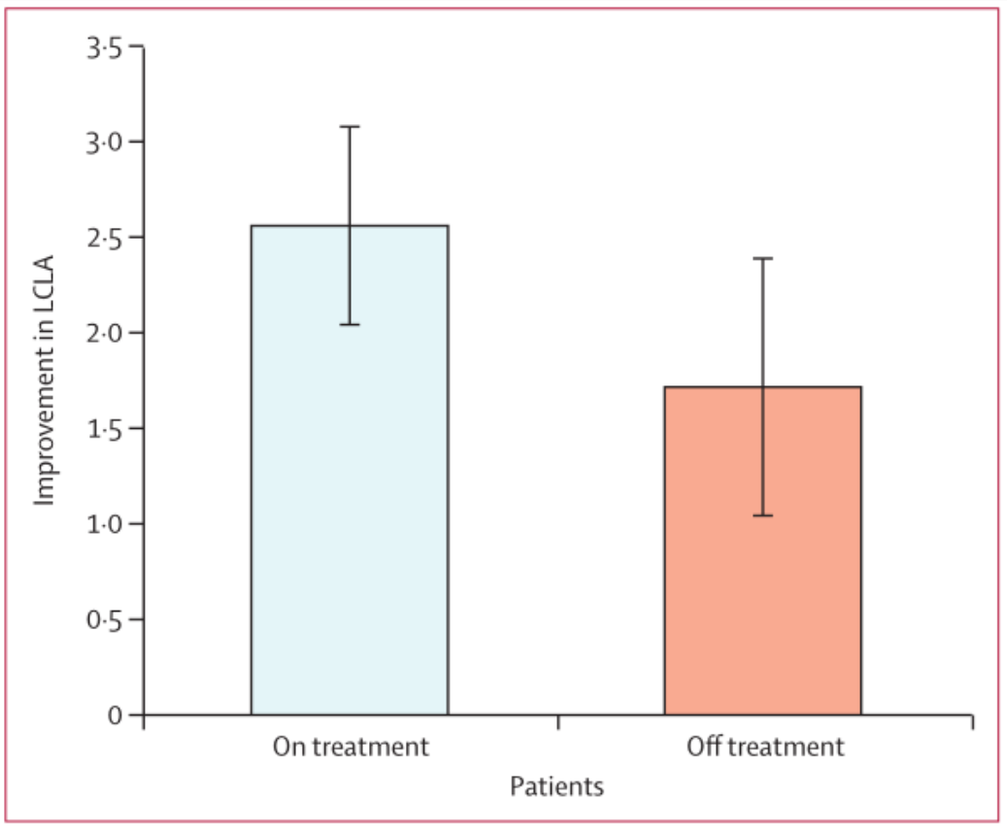



***Figure 3:*** **Association of clemastine fuma**
**on LCLA testing**
Change is in number of letters identified c
epochs combined. p=0·085. LCLA=low-co

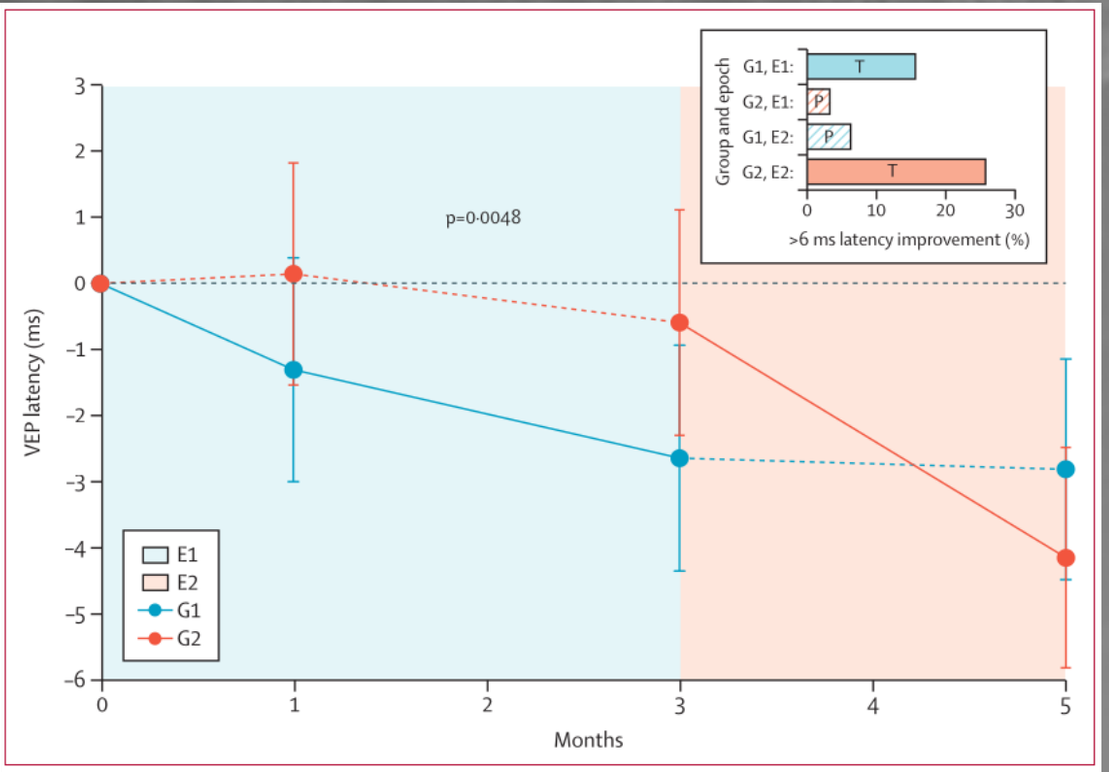



***Figure 2:*** **Association of clemastine fumarate treatment with VEP latency delay in patients with chronic optic neuropathy**

estimates of means are represented by dots
mepoint). Solid line is on-treatment and
lue shaded area is epoch 1 and orange
ver (with assumption of carryover). The inset
ency delay. VEP=visual-evoked potential.
nt period. P=placebo period.

Patients in both groups exhibited shortening of P100 latency while on the active compound. The primary prespecified efficacy endpoint for the trial was met with reduction of latency delay of 1·7 ms/eye (95% CI 0·5–2·9; p=0·0048) in the crossover model.

# Limitations of (most) trials

- One model: Optic Neuritis
- Outcome measure: VA, pVEP

# Treatment failures

- Issues with primary outcome measure
  - In ON this is high contrast VA (ceiling effect)
- Non-responders
  - Nothing left to remyelinate (axonotmesis)

# To be covered

- Background on remyelination
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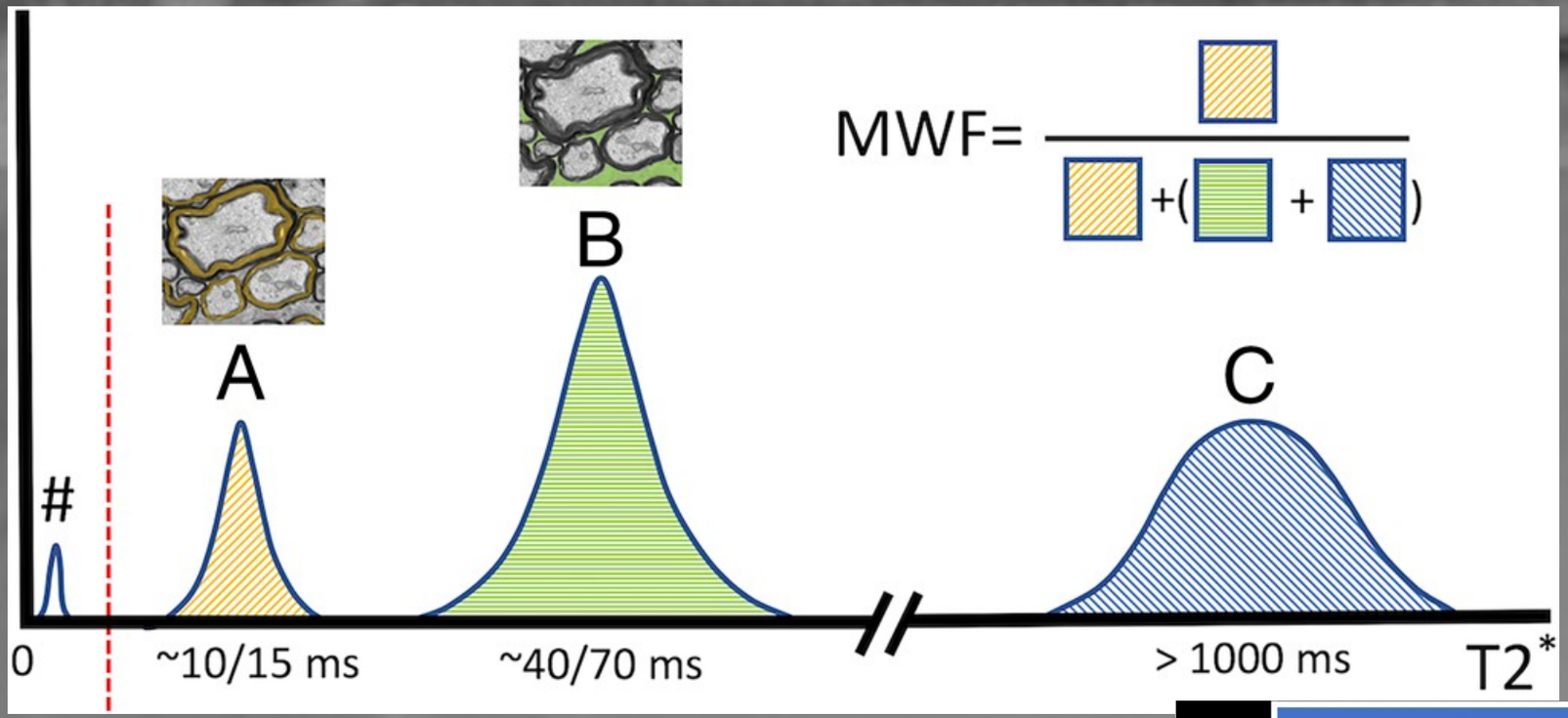
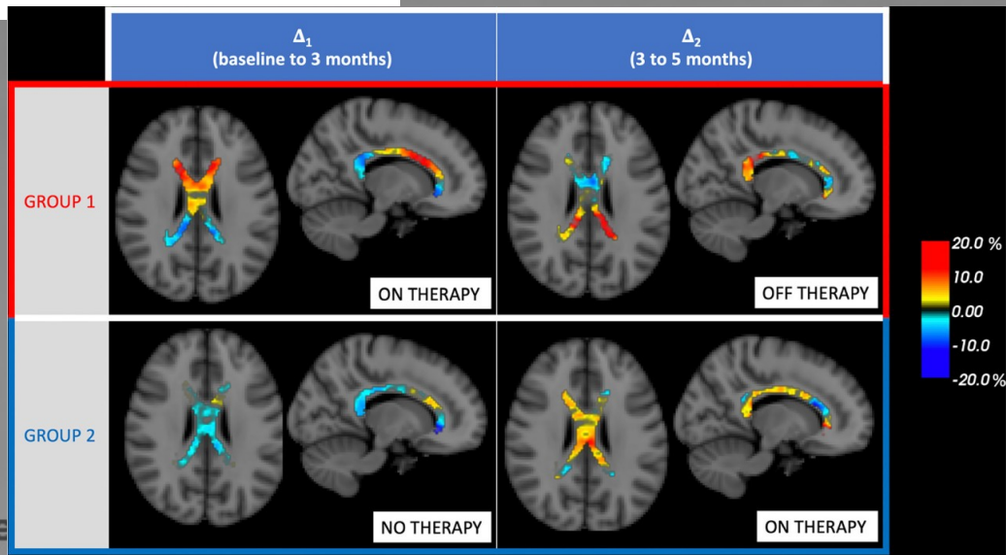
# Myelin Water Fraction (MWF)





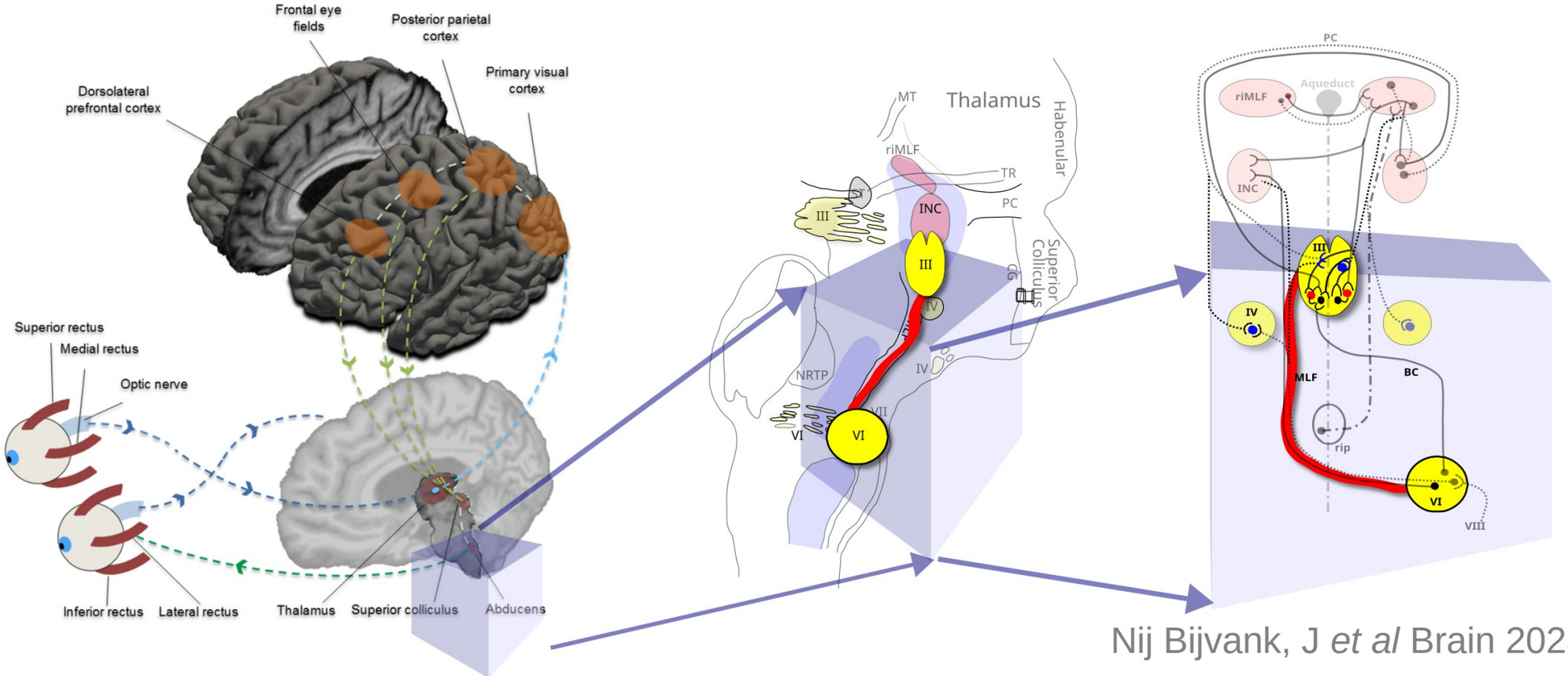

Caverzasi, E *et al* PNAS 2023

Expe

https://doi.org/10.1093/brain/awac474 BRAIN 2023: 146; 2476–2488 | 2476

BRAIN
ORIGINAL ARTICLE

# A novel eye-movement impairment in multiple sclerosis indicating widespread cortical damage




Nij Bijvank, J *et al* Brain 2023

# INO

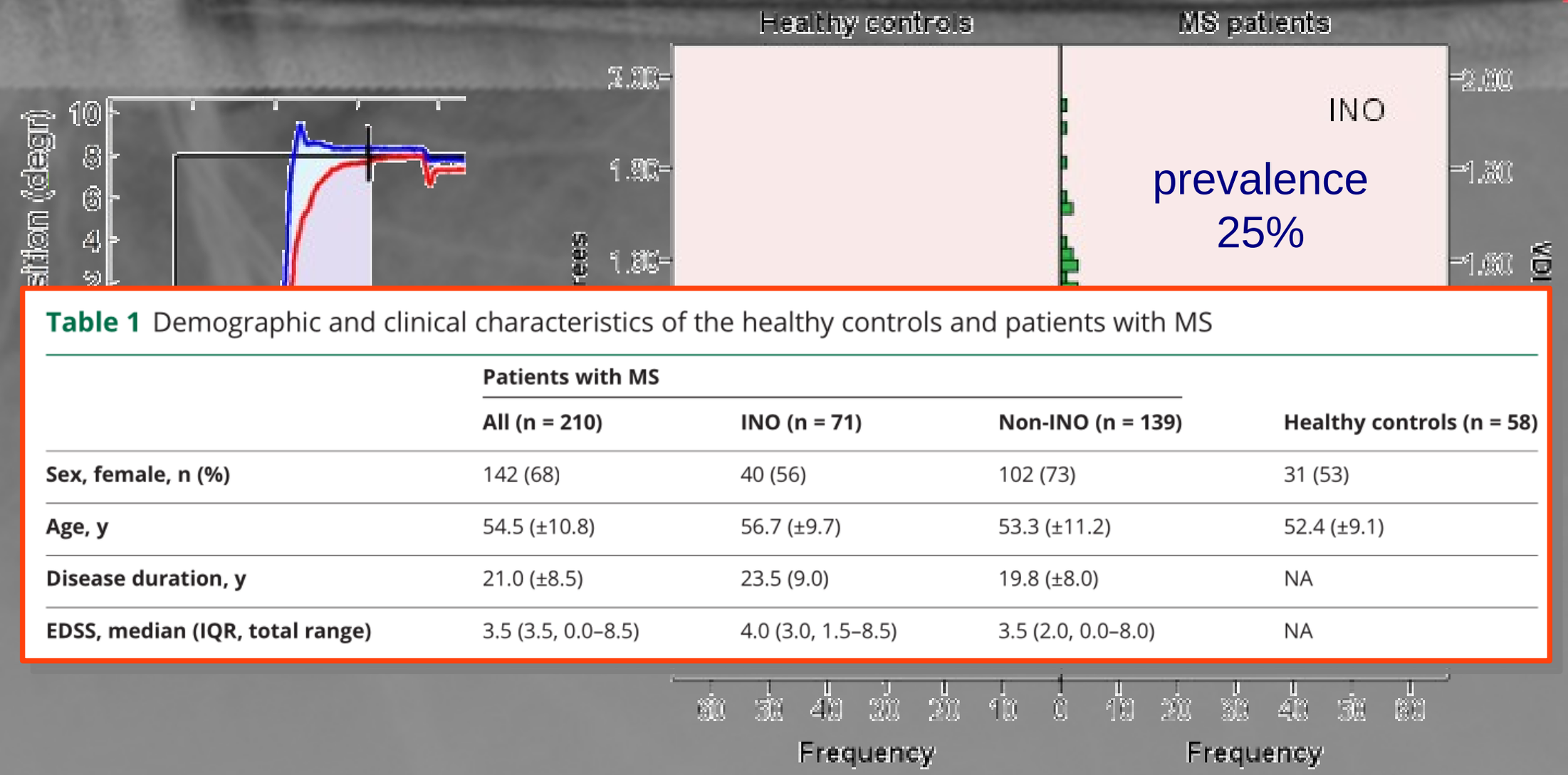



**Table 1** Demographic and clinical characteristics of the healthy controls and patients with MS

| | Patients with MS | | | |
|---|---|---|---|---|
| | **All (n = 210)** | **INO (n = 71)** | **Non-INO (n = 139)** | **Healthy controls (n = 58)** |
| **Sex, female, n (%)** | 142 (68) | 40 (56) | 102 (73) | 31 (53) |
| **Age, y** | 54.5 (±10.8) | 56.7 (±9.7) | 53.3 (±11.2) | 52.4 (±9.1) |
| **Disease duration, y** | 21.0 (±8.5) | 23.5 (9.0) | 19.8 (±8.0) | NA |
| **EDSS, median (IQR, total range)** | 3.5 (3.5, 0.0–8.5) | 4.0 (3.0, 1.5–8.5) | 3.5 (2.0, 0.0–8.0) | NA |

Nij Bijvank, J *et al* Neurology 2019

# INO in population based birth cohort (1966)

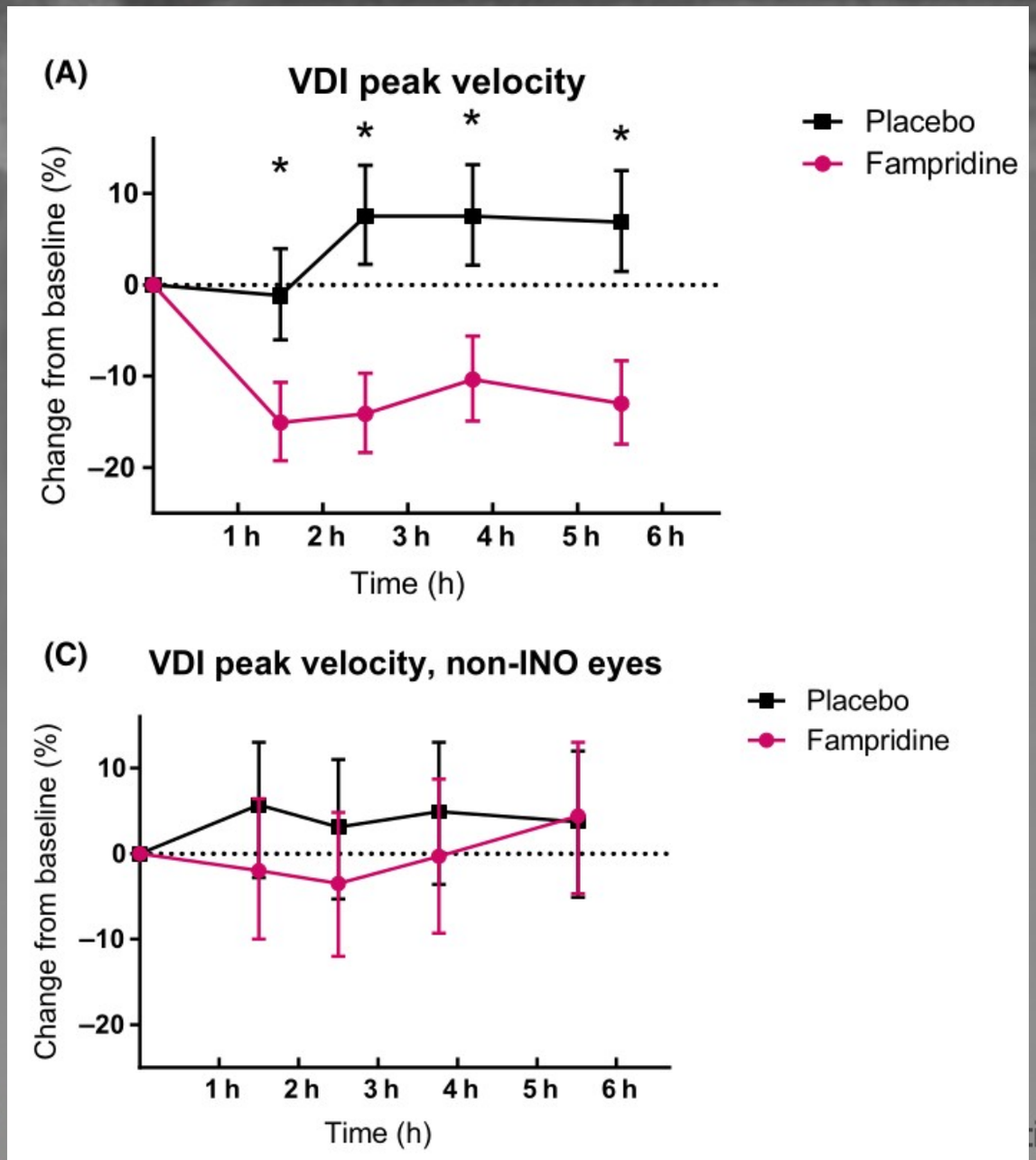
**INO prevalence in MS 24%**

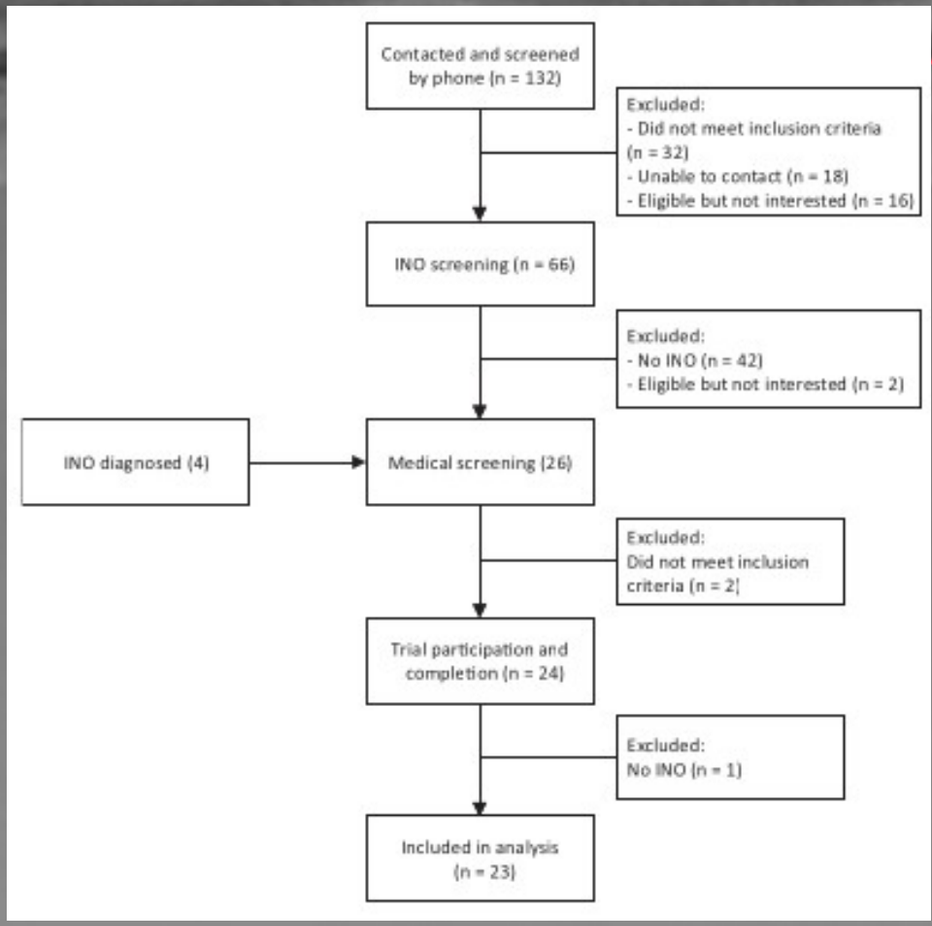
**Table 1**
Demographic and clinical characteristics of individuals with MS and healthy controls.

| | Individuals with MS Overall, $N = 220$[1] | INO, $N = 53$[1] | Non-INO, $N = 167$[1] | p-value[2] | Healthy controls $N = 110$[1] |
|---|---|---|---|---|---|
| **Sex, female** | 160 (73%) | 30 (57%) | 130 (78%) | **0.002** | 80 (73%) |
| **Disease course**[a] | | | | 0.129 | NA |
| PPMS | 32 (15%) | 9 (17%) | 23 (14%) | | NA |
| SPMS | 48 (22%) | 16 (31%) | 32 (19%) | | NA |
| RRMS | 138 (63%) | 27 (52%) | 111 (67%) | | NA |
| **Disease duration, y** | 16 (9) | 16 (10) | 16 (9) | 0.915 | NA |
| **Current DMT use** | 95 (43%) | 27 (51%) | 68 (41%) | 0.190 | NA |
| **EDSS** | 3.5 (2.5–4.0) | 4.0 (3.0–4.5) | 3.5 (2.5–4.0) | **0.044** | NA |
| **SDMT**[b] | 52 (10) | 49 (10) | 53 (10) | **0.046** | NA |
| **NHPT (*sec*)**[c] | 21.59 (19.41–24.37) | 22.20 (20.50–26.27) | 21.41 (19.00–24.02) | **0.015** | NA |
| **T25-FW (*sec*)**[d] | 4.85 (4.15–6.20) | 5.15 (4.40–7.11) | 4.80 (4.05–6.12) | 0.136 | NA |
| **HCVA, mean ODS**[e] | 54 (50–60) | 54 (48–58) | 54 (50–60) | 0.270 | NA |
| **LCVA, mean ODS**[f] | 29 (22–35) | 26 (20–34) | 29 (22–35) | 0.325 | NA |
| **History of optic neuritis** | 86 (39%) | 25 (47%) | 61 (37%) | 0.167 | NA |
| **History of vascular risk factors**[g] | 50 (23%) | 9 (17%) | 41 (25%) | 0.252 | 22 (20%) |
| **History of vascular events**[h] | 5 (2.3%) | 1 (1.9%) | 4 (2.4%) | >0.999 | 0 (0%) |

Hof, S *et al* MSRD 2022

# Can we predict remyelination treatment response?




Kawita, M.S.K. *et al* CNSNT 2018

# To be covered

- Background on remyelination
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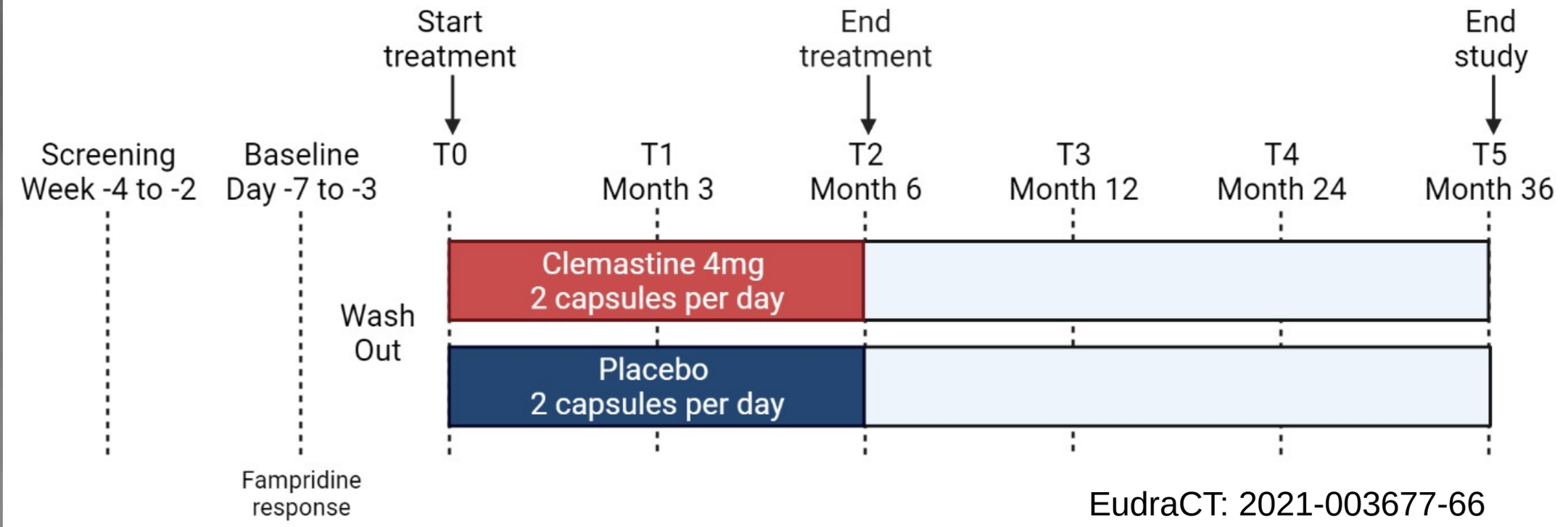
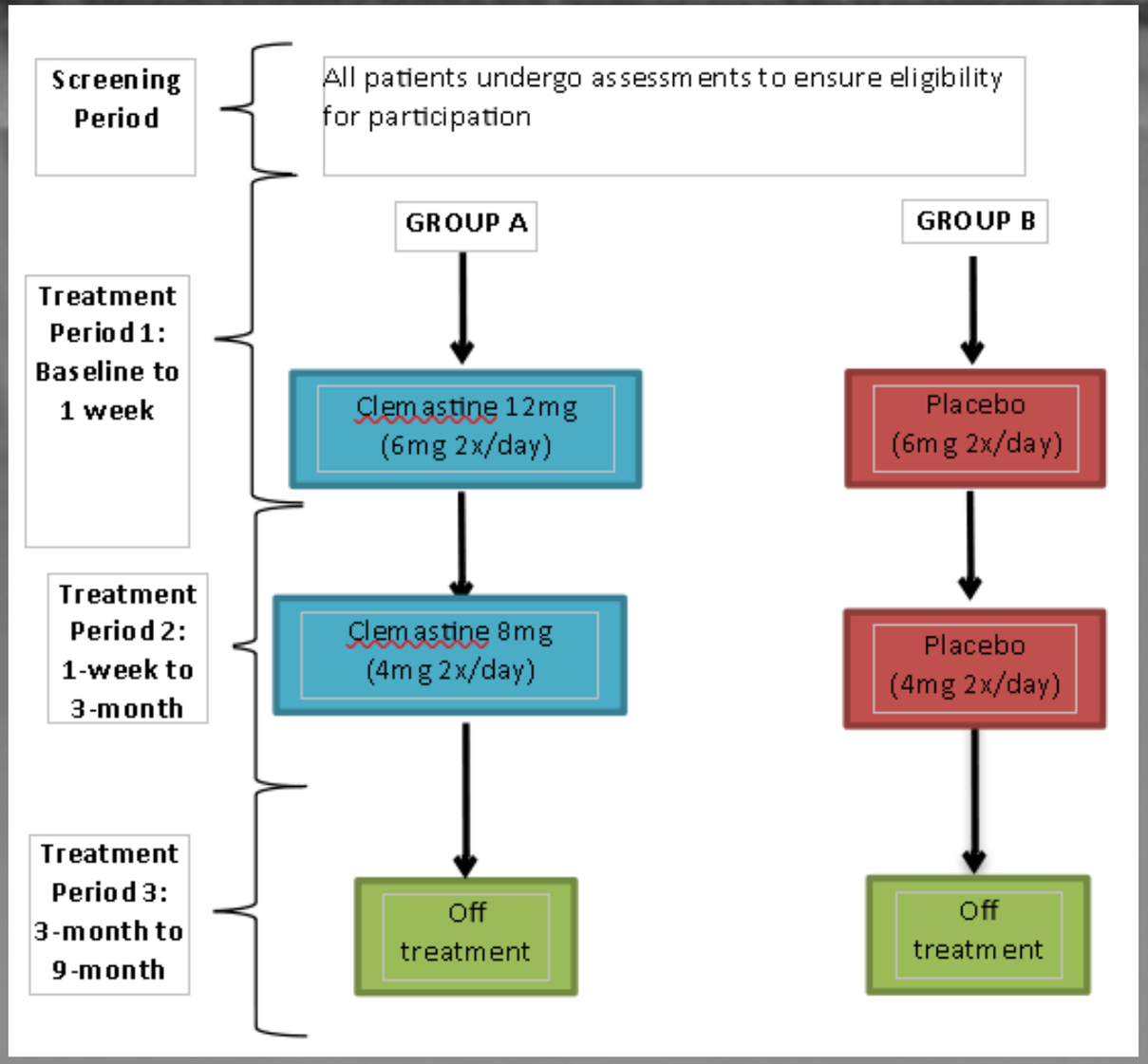
# RESTORE trial




EudraCT: 2021-003677-66
ClinicalTrials.gov: NCT05338450

Hof, S et al. [under revision]

# RECOVER trial




ClinicalTrials.gov: NCT00896220

# To be covered

- Background on remyelination
- The key trial in humans
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# Summary

## RemyelINatiON

- Drug discovery strategy (high throughput)
- Chose a safe option (clemastine)
- Afferent visual pathway model (VEP)
- Efferent visual pathway model (VDI)
- Two model confirmation (RCT)
- Re-consider role for PET-MRI

# Wielkie dzięki