MASSACHUSETTS GENERAL HOSPITAL
NEUROLOGY

HARVARD MEDICAL SCHOOL

Experimental Treatments for MOG Antibody Disease

Michael Levy, MD, PhD
Associate Professor
Research Director, Division of Neuroimmunology and Neuroinfectious Disease

December 7, 2022

MOG: Acute vs. Preventive

Acute

Preventive

Acute: Standard of Care

Methylprednisolone IV 1000 mg daily x5 days with a 2-3 month taper

OR

IVIG 2 grams/kg ideal body weight
(no steroids)

IVIG for acute MOG relapses

Total	39
Attack phenotype (N, %)	
Unilateral ON	14 (35.9)
Bilateral ON	5 (12.8)
Myelitis	3 (7.7)
Brainstem syndrome	1 (2.6)
Encephalitis	1 (2.6)
ADEM	8 (20.5)
Multifocal	7 (17.9)
IVIG treatment dose (protocol) (N, %)	
0.8 g/kg (0.4g/kg x 2 days)	1(2.6)
1 g/kg (1 gr/kg x 1 day)	1(2.6)
1.2 g/kg (0.4g/kg x 3 days)	3 (7.7)
1.32 g/kg (0.66g/kg x 2 days)	1(2.6)
1.6 g/kg (0.4 gr/kg x 4days)	1 (2.6)
1.98 g/kg (0.66g/kg x 3 days)	2(5.2)
2 g/kg (0.4g/kg x 5 days)	17 (43.6)
2 g/kg (1 gr/kg x 2 days)	12 (30.8)
2.4 gr/kg (0.4g/kg x 6 days)	1(2.6)
Additional treatments (N, %)	
None	5 (12.8)
IVMP	15 (38.5)
IVMP +oral CS	5 (12.8)
IVMP + TPE	9 (23.1)
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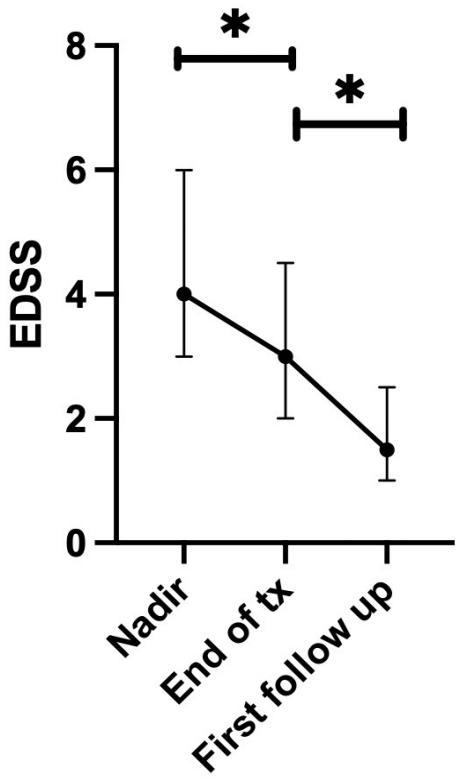
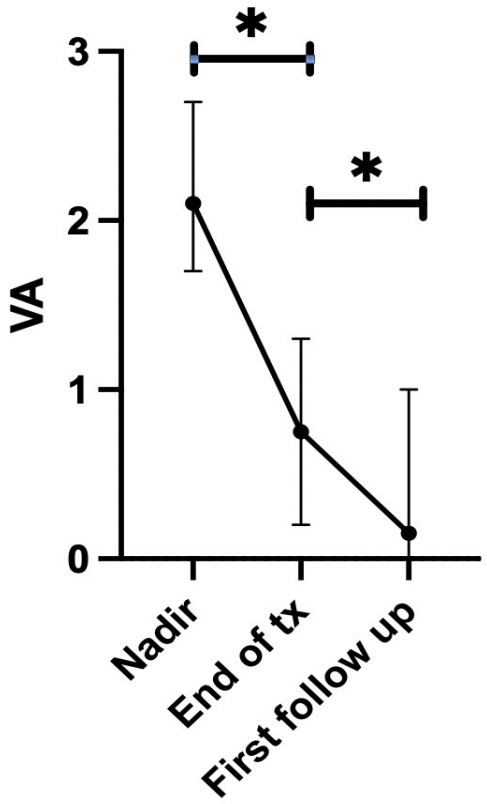
Results





EDSS = Expanded Disability Status Scale VA = visual acuity

Preventive – Off-label

- IVIG 1 g/kg q4w = 60%
- IVIG 2 g/kg q4w = 80%
- SCIG 0.4 g/kg qweek

Goal: Suppress disease long enough that MOG goes away

- Cellcept 600 mg/m2 BSA daily

When all else fails: prednisone 20 mg daily

MOG trials

- Rozanolixizumab (launched)
- Satralizumab (launched)
- Tolebrutinib (planned Q1 2023)

Rozanolixizumab Study MOG001

cosMOG

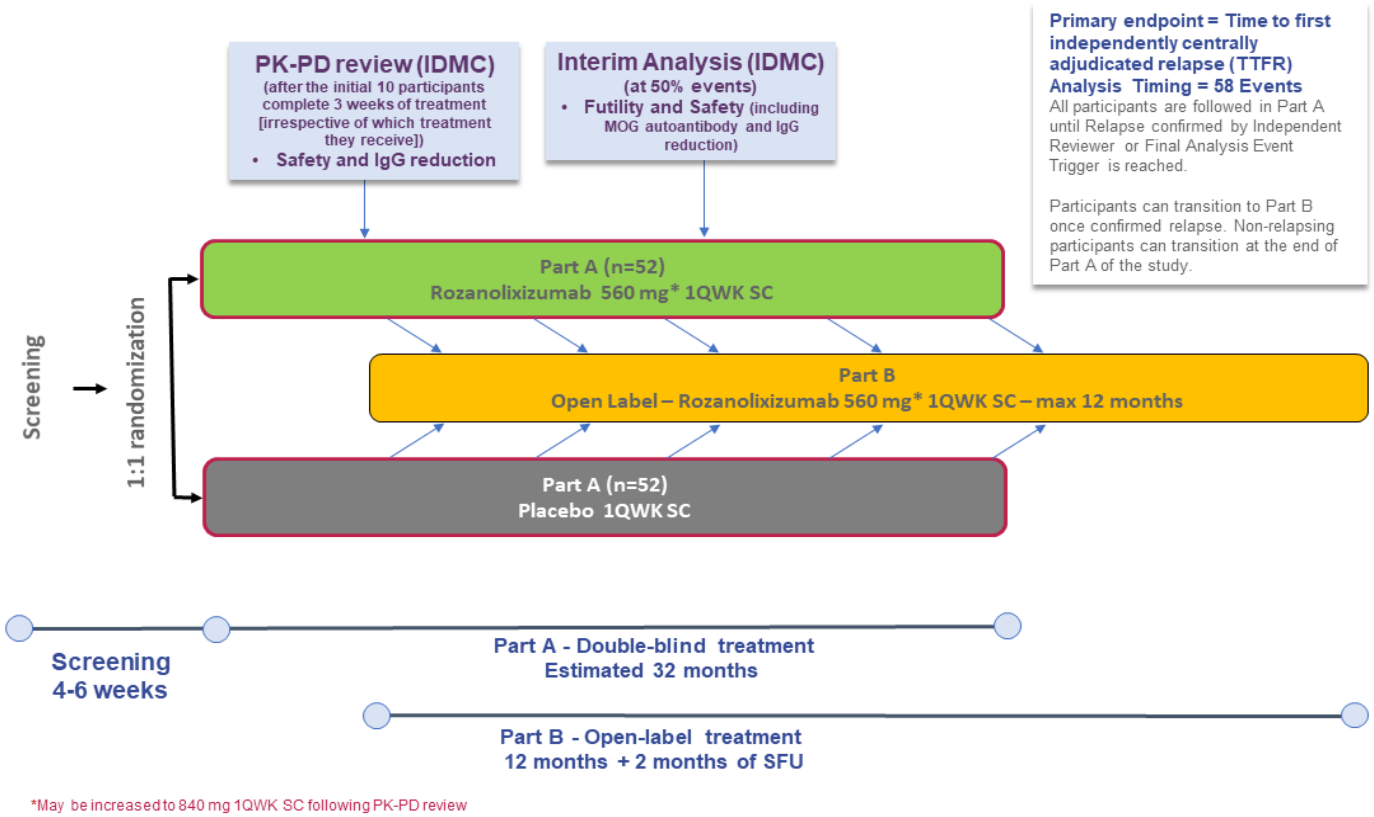
cosMOG

Study Design

- **104 participants to be enrolled at approximately 65-70 sites**
- **Double-blind Period (flexible length) + Open-label Period (12 months)**
- **Participant can transition to OLE after a relapse confirmed by adjudication committee**
- **DB-Part will be closed once 58 relapse events have been confirmed**
- **SFU (8 weeks post last IMP)**
- **IDMC:**
  - PK-PD Review after 10 participants completed 3 weeks treatment (possible dose increase)
  - Interim Analysis after 50% events reached

IDMC: Independent Data Monitoring Committee, IMP: Investigational Medicinal Product; OLE: Open Label Extension; PD: Pharmacodynamic; PK: Pharmacokinetic, SFU: Safety Follow-Up

Study Design



IDMC: Independent Data Monitoring Committee, IgG: immunoglobulin G; IMP: Investigational Medicinal Product; OLE: Open Label Extension; PD: Pharmacodynamic; PK: Pharmacokinetic, SC: subcutaneous, SFU: Safety Follow-Up

Inclusion criteria

Age

1. Participant must be **≥18 to ≤89 years of age**, at the time of signing the informed consent.
   Japan-specific: Participant must be ≥18 years of age at the time of signing the informed consent. If a participant is <20 years of age, written informed consent will be obtained from both the participant and the legal representative.

Type of Participant and Disease Characteristics

2. Participant must have a **history of MOG-AD** with any of the following clinical presentations:
   - **Optic neuritis (single, recurrent, or simultaneous bilateral)**
   - **Transverse myelitis (including LETM)**
   - **Acute disseminated encephalomyelitis or MOG antibody-associated encephalitis, brain stem encephalitis**
   - **Combined presentations**
3. **Positivity for serum MOG-IgG antibodies** using cell-based assay at Screening.
4. Participant has **history of relapsing MOG-AD with at least 1 documented relapse over the last 12 months** prior to randomization.
5. Participant must **be clinically stable** at the time of the Screening Visit and during the Screening Period.

Schedule of Activities

- Please pay attention to footnotes
- Gray shaded visits can be done at home if participant and investigator agrees. A checklist has to be completed prior to start of home visits (→ **Section 8**)
- Prednisolone administration for first 4 weeks of DB Period (and possibly also at start of OLE Period) (→ **Section 6.5.1.1**)
- **Required order of assessments:**
  Questionnaires (always first)
  Examinations
  Lab samples
  IMP administration

	Screening		Baseline			Double-Blind Treatment Period[a]									
Week (W)	W -6 to -4		W1			W2	W3		W4	W5	W6	W7	W8	W9 W10 W11	W12
Visit (V) Procedure	SC		V1A	V1B	V1C	V2	V3A	V3B	V4	V5	V6	V7	V8	V9 V01 V11	V12
			D1 Pre	D3±1	D6±1		Pre	D17±1							
Informed consent	X														
Verification of inclusion/exclusion criteria	X		X[b]												
Call or enter IRT to register the visit	X		X			X	X		X	X	X	X	X	X	X
Demographic and BL characteristics	X		X												
Weight	X		X												X
Prior/concomitant medication review	X		X	X	X	X	X	X	X	X	X	X	X	X	X
General medical/procedure history (including psychiatric and MOG relapse history)	X														
C-SSRS[c]	X		X			X	X		X	X	X		X		X
Chest x-ray[d]	X														
IGRA TB test[e]	X														
TB signs and symptoms questionnaire	X		X												X
12-lead ECG	X		X			X	X		X						X
Full physical examination	X		X												
Brief physical examination						X	X		X						X
Full neurological examination	X		X												
FSS/EDSS			X						X						X

ADA: Anti-drug Antibody; AE: Adverse event; DB: Double-blind, EDSS: Expanded Disability Status Scale ; FSS: Functional Systems Score, HIV: human immune deficiency virus; IgG: Immunoglobulin G; IMP: Investigational Medicinal Product; OLE: Open-Label Extension; PK: Pharmacokinetic

Relapse Definitions and Assessments

Relapse Definition	Relapse Assessment
Optic neuritis	• MRI • Ophthalmological examination
Transverse myelitis	• MRI • FSS • EDSS
MOG encephalitis/ Acute disseminated encephalomyelitis	• MRI • EDSS

Relapse Assessment: Description Narrative

- A short narrative describing the relapse will be entered in the CRF
- This is an opportunity to provide all the clinically relevant details that may be relevant for the evaluation of the relapse, and that are not captured elsewhere (EDSS, ophthalmological assessments)
- **Examples:** time course, impairment of consciousness, seizures, neuropathic pain, anatomical distribution of sensory deficits, eye pain

CRF, case report form; EDSS, Expanded Disability Status Scale; FSS, Functional Systems Scores, MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging.

METEOROID

Pivotal randomized, phase 3, double-blind, placebo-controlled study of satralizumab in adults and adolescents with MOGAD

Michael Levy, MD, PhD

Associate Professor, Harvard Medical School
Director, Neuroimmunology Clinic and Research Laboratory
Research Director, Division of Neuroimmunology and Neuroinfectious Disease
Department of Neurology, Massachusetts General Hospital

MOG Therapeutics Roundtable Agenda, 29 and 30 September 2022, Cambridge, Massachusetts

ucb parexel

Clinical rationale for IL-6 inhibition in MOGAD

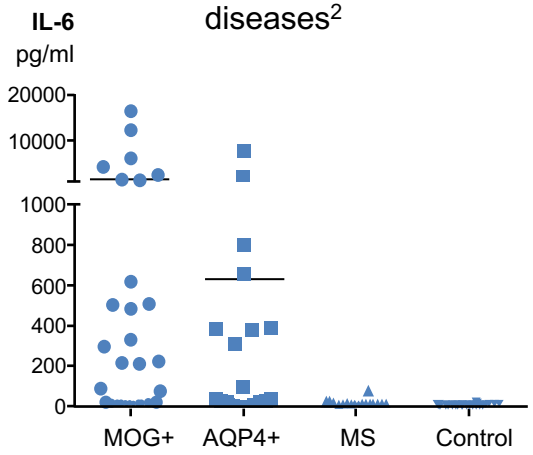
Pre-clinical evidence

- IL-6 levels are increased in the CSF and possibly serum of MOGAD patients **(Figure 1)**[1–4]
- Peripheral Th17-cell subset increases during MOGAD attacks and decreases in the remission phase[5]

Clinical evidence

- The IL-6 receptor (IL-6R) antagonist tocilizumab, used off-label, was shown to be effective in >20 patients with MOGAD[6–13]
- Satralizumab significantly reduced relapse risk in AQP4-IgG+ NMOSD, an autoantibody-driven disease that is clinically similar to MOGAD[14,15]
- Satralizumab was investigate in both adolescents and adults with NMOSD, with up to 7 years of exposure[16,17]

Figure 1. CSF IL-6 levels in patients with demyelinating diseases[2]



Adapted from Kaneko et al. J Neurol Neurosurg Psychiatry 2018[2]

AQP4-IgG+, aquaporin-4 immunoglobulin G seropositive; CSF, cerebrospinal fluid; IL-6, interleukin 6; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

1. Kothur K et al. *PLoS One* 2016;11:e0149411. 2. Kaneko et al. *J Neurol Neurosurg Psychiatry* 2018;89:927-936. 3. Serguera C et al. *J Neuroinflammation* 2019;16:244. 4. Hofer LS et al. *Mult Scler J Exp Transl Clin* 2019;5:2055217319848463. 5. Liu J et al. *J Neurol Neurosurg Psychiatry*. 2020;91:132-139. 6. Hayward-Koennecke H et al. *Neurology* 2019;92:765-767. 7. Novi G et al. *Mult Scler Relat Disord* 2019;27:312-314. 8. Lotan I et al. *Mult Scler Relat Disord* 2019;39:101920. 9. Jelcic et al. *J Neuroophthalmol* 2019;39(1):3-7. 10. Rigal J et al. *Mult Scler Relat Disord* 2020;46:102483. 11. Elsbernd PM et al. *Mult Scler Relat Disord*. 2021;48:102696. 12. Masuccio FG, et al. *Mult Scler Relat Disord* 2020;46:102592.13. Ringelstein M, et al. *Neurol Neuroimmunol Neuroinflamm* 2022;9:e1100. 14. Yamamura T et al. *N Engl J Med* 2019;381:2114-2124. 15. Traboulsee A, et al. *Lancet Neurol* 2020;19(5):402–12. 16. Yamamura T, et al. *Mult Scler Relat Disord* 2022;66:104025. 17. Kleiter I, et al. *Neurol Neuroimmunol Neuroinflamm* 2022 (under review).

METEOROID: Phase 3, double-blind study of satralizumab (± IST)

Event-driven DB treatment period:

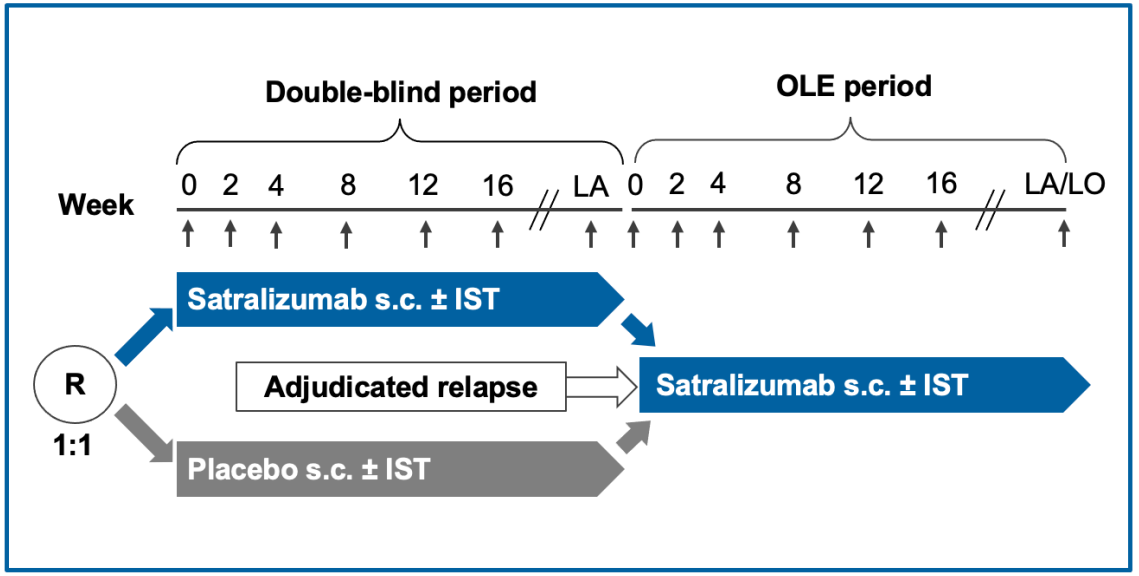
- Ends when 28 adjudicated MOGAD relapses are observed (expected 44 months after FPI)

OLE period:

- Approximately 24 months

Safety follow up:

- 12 weeks for adults and 24 weeks for adolescents



DB, double-blind; CEC, Clinical Endpoint Committee; FPI, first patient in; IST, baseline/background immunosuppressive therapy; LA/LO, last administration/observation; OLE, open-label extension.

METEOROID study: Patient population

Target population: 152 adults and adolescents (age ≥12 years) with **relapsing MOGAD**

Eligibility requirements

- ✓ Confirmed MOGAD diagnosis, with MOG-IgG seropositivity confirmed by CBA
- ✓ ≥2 MOGAD attacks ≤24 months prior to screening
- ✓ Attack phenotypes consistent with MOGAD
- ✓ Exclusion of alternative diagnoses, including MS, NMDAR seropositive autoimmune encephalitis, and AQP4-IgG seropositive NMOSD
- ✓ Treatment prior to screening is one of:
  - a) No ongoing chronic immunosuppressive treatment for MOGAD
  - b) Ongoing treatment with oral corticosteroids (OCS), azathioprine (± OCS), or mycophenolate mofetil (± OCS)
- ✓ No evidence of active or recurrent infections, including TB and acute or chronic hep B and C

AQP4-IgG; aquaporin-4 immunoglobulin G; CBA, cell-based assay; MOG-IgG, myelin oligodendrocyte glycoprotein immunoglobulin G; NMDAR, N-methyl-D-aspartate receptor; NMOSD, neuromyelitis optica spectrum disorder; OCS, oral corticosteroids; TB, tuberculosis.

METEOROID study: Endpoints

1

Primary endpoint

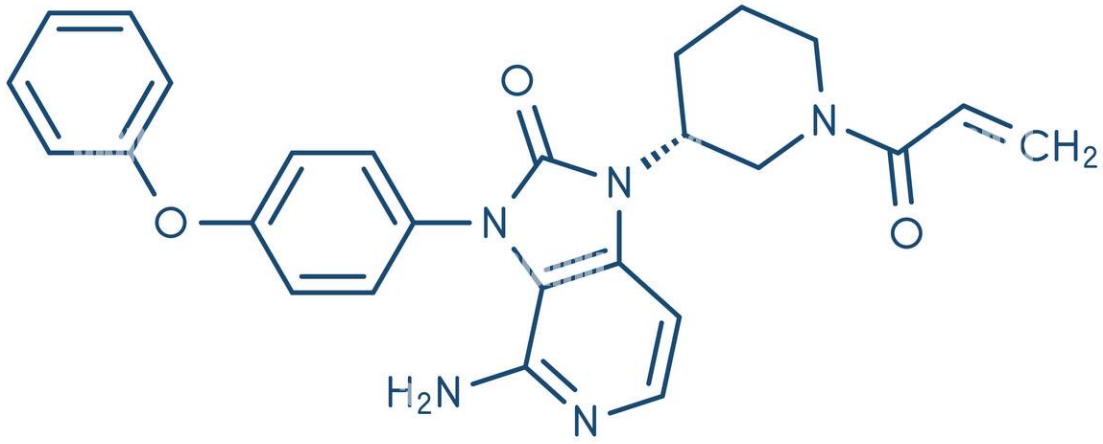
Time from randomization to the first MOGAD relapse in the double-blind treatment period, as determined by an independent clinical adjudication committee (Clinical Endpoint Committee [CEC])

2

Key secondary endpoints *(in hierarchical order)*

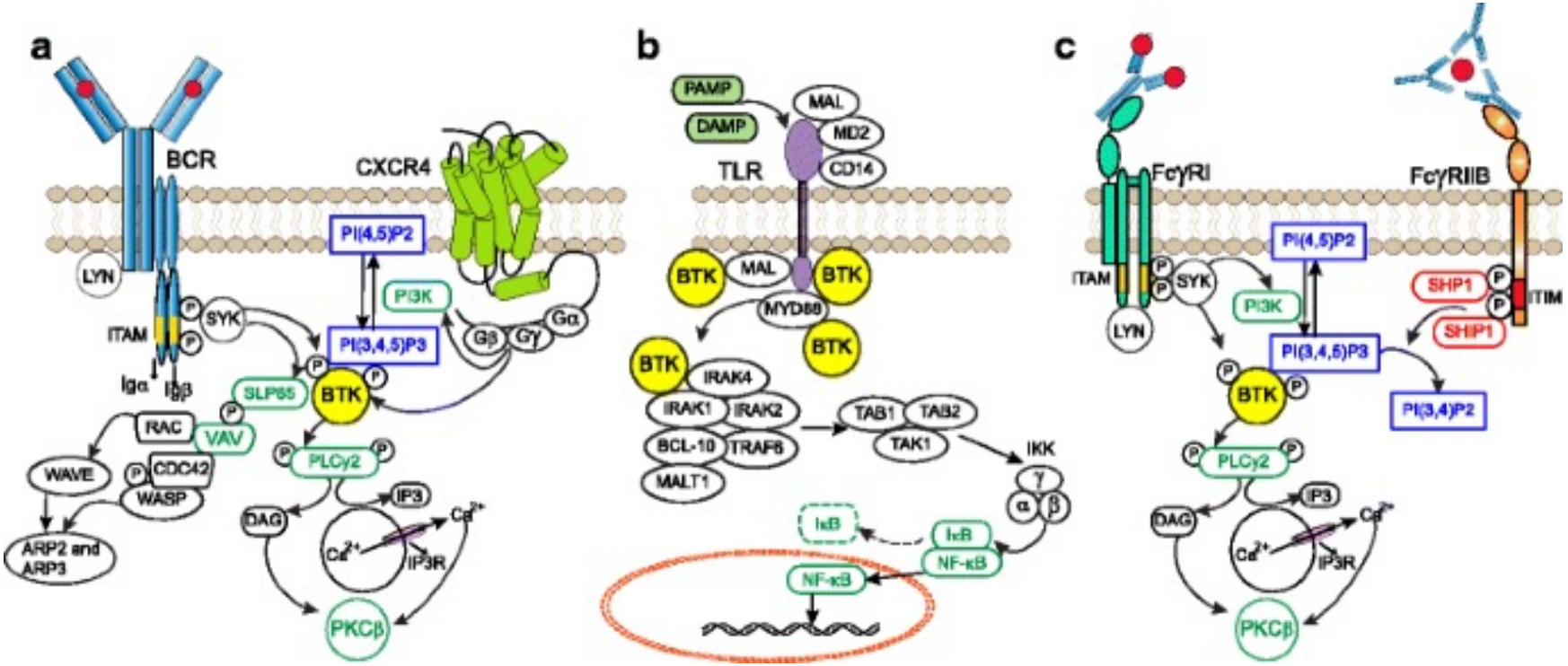
1. Annualized rate of adjudicated MOGAD relapses
2. Annualized rate of active lesions on MRI of the neuroaxis
3. Proportion of participants receiving rescue therapy
4. Annualized rate of inpatient hospitalizations
   (defined as more than an overnight stay, excluding those for elective procedures)

Tolebrutinib



tolebrutinib

Bruton's Tyrosine Kinase



Pal Singh, S., Dammeijer, F. & Hendriks, R.W. Role of Bruton's tyrosine kinase in B cells and malignancies. *Mol Cancer* **17**, 57 (2018).

Phase 2 trial in Multiple Sclerosis

ARTICLES | VOLUME 20, ISSUE 9, P729-738, SEPTEMBER 01, 2021

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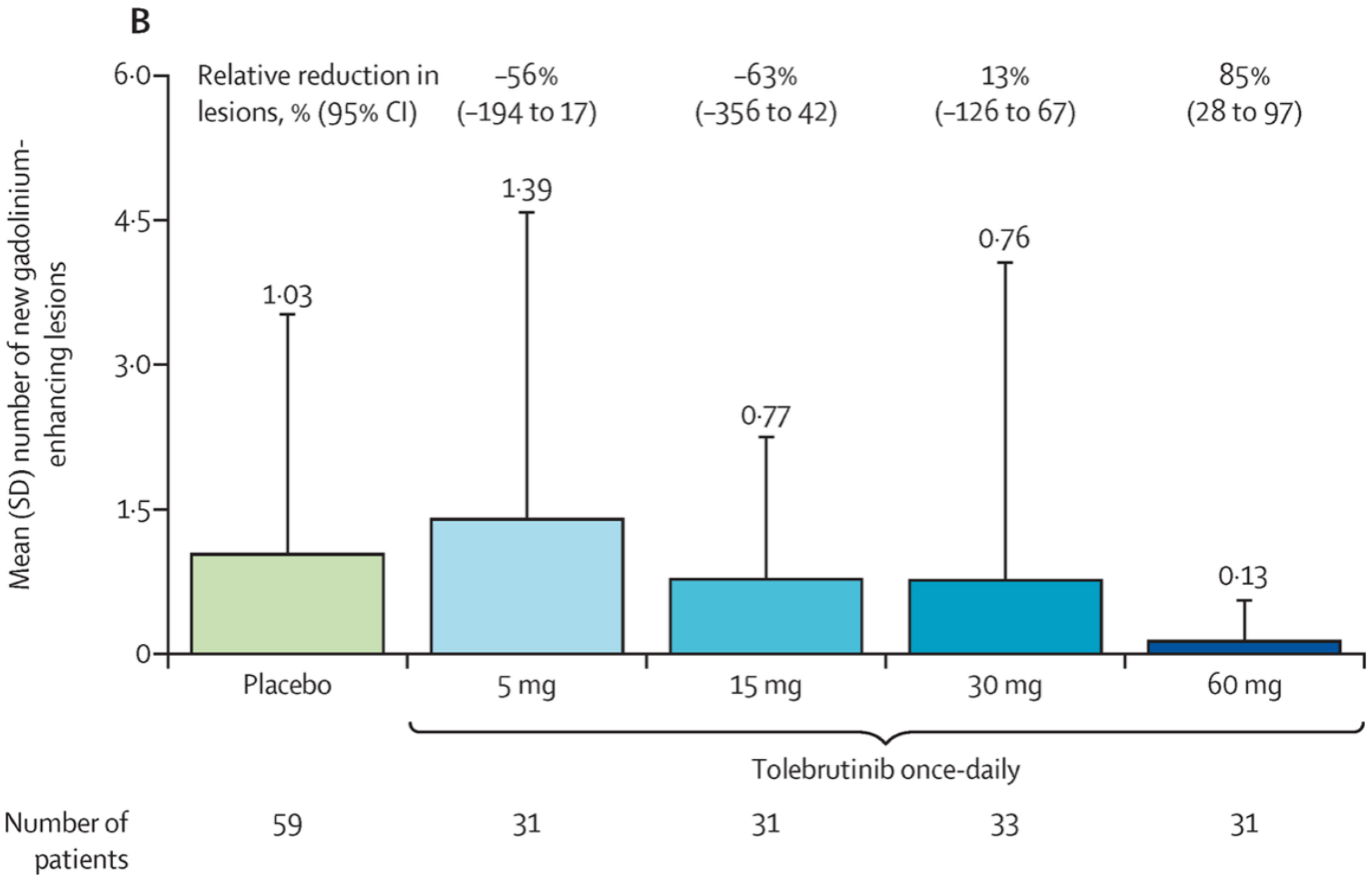
Safety and efficacy of tolebrutinib, an oral brain-penetrant BTK inhibitor, in relapsing multiple sclerosis: a phase 2b, randomised, double-blind, placebo-controlled trial

Prof Daniel S Reich, MD • Prof Douglas L Arnold, MD • Patrick Vermersch, MD • Prof Amit Bar-Or, MD • Robert J Fox, MD • Andre Matta, MD • et al. Show all authors • Show footnotes

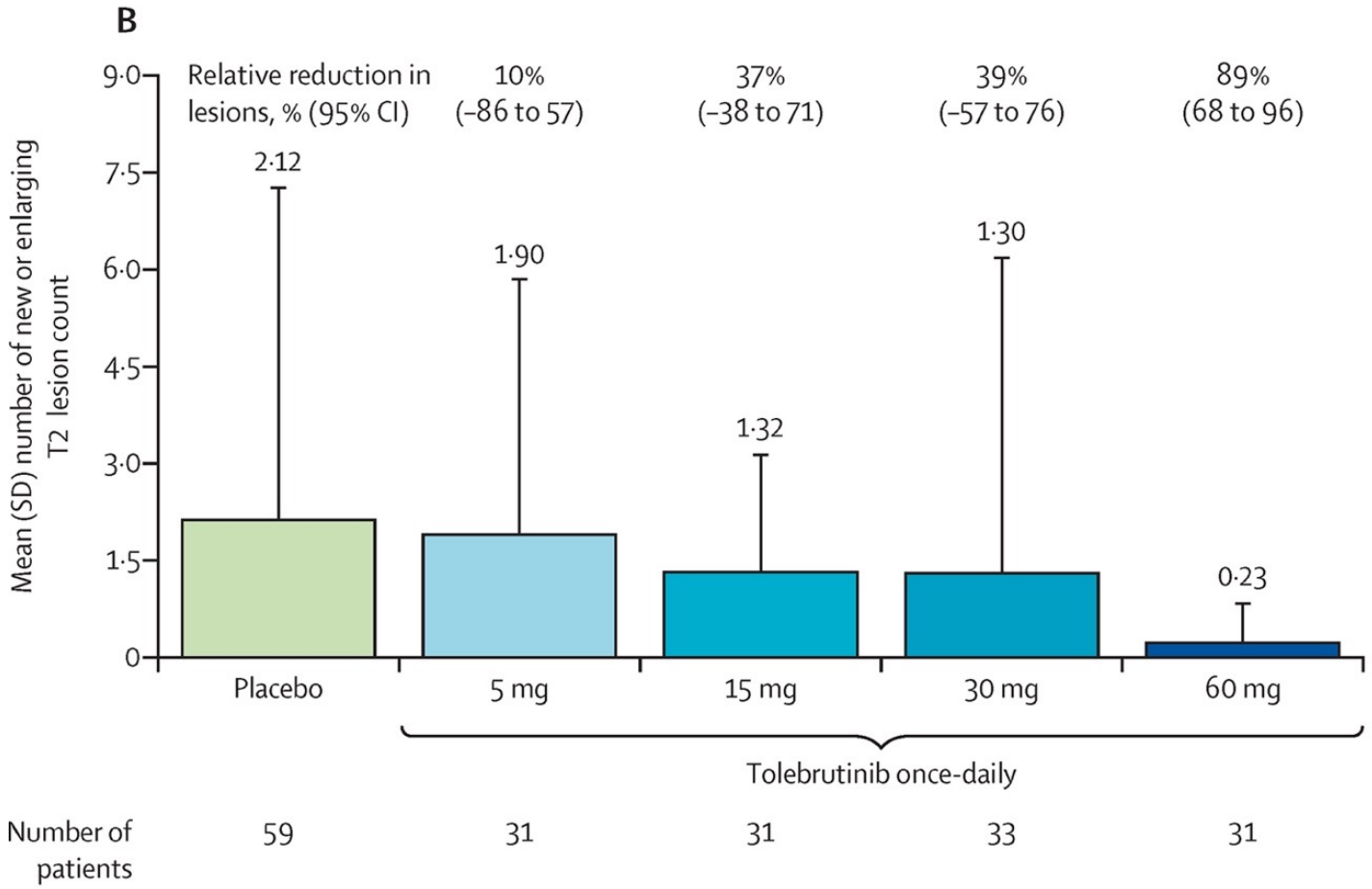
Published: September, 2021 • DOI: https://doi.org/10.1016/S1474-4422(21)00237-4 • Check for updates

PlumX Metrics

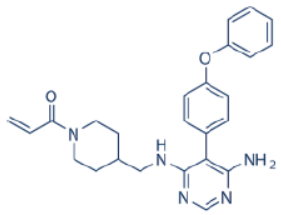
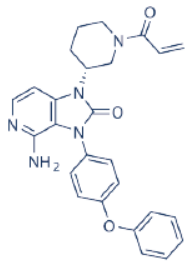
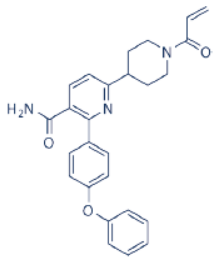
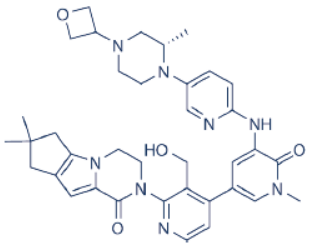
Phase 2 trial in Multiple Sclerosis



Phase 2 trial in Multiple Sclerosis



Other BTK inhibitors in MS

TABLE. COMPARISON OF BRUTON TYROSINE KINASE INHIBITOR PHARMACOLOGY				
	Evobrutininb (M-251) (PRN2246)	**Tolebrutinib (SAR442168)**	**Orelabrutinib (ICP-022)**	**Fenebrutinib (GDC-0853)**
Structure				
Molecular weight	429.51[24]	455.51[24]	427.9[25]	664.80[24]
Chemical bond with BTK10	Covalent, irreversible	Covalent, irreversible	Covalent, irreversible	Noncovalent, reversible
Inhibition site	Kinase domain C481 residue	Kinase domain C481 residue	Kinase domain C481 residue	SH2 domain K430 residue, kinase domain M 477 and D539 residues
IC50 (nM)[a]	37.97	0.4-0.79	1.6	2.37
Inhibition of other tyrosine kinases	Minimal, targets BTK selectively[7]	Binds 12 of 250 tyrosine kinases at 1 mcMol[9]	Best selectivity, BTK only; > 90% inhibition[25]	Targets 2 of 286 kinases[7]

Abbreviations: BTK, Bruton tyrosine kinase; BTKI, BTK inhibitor; IC50, half-maximal concentration. [a]The IC50 for the BTKIs of interest vary depending on the type of used cells to determine the inhibition constant; however different papers report comparable values.

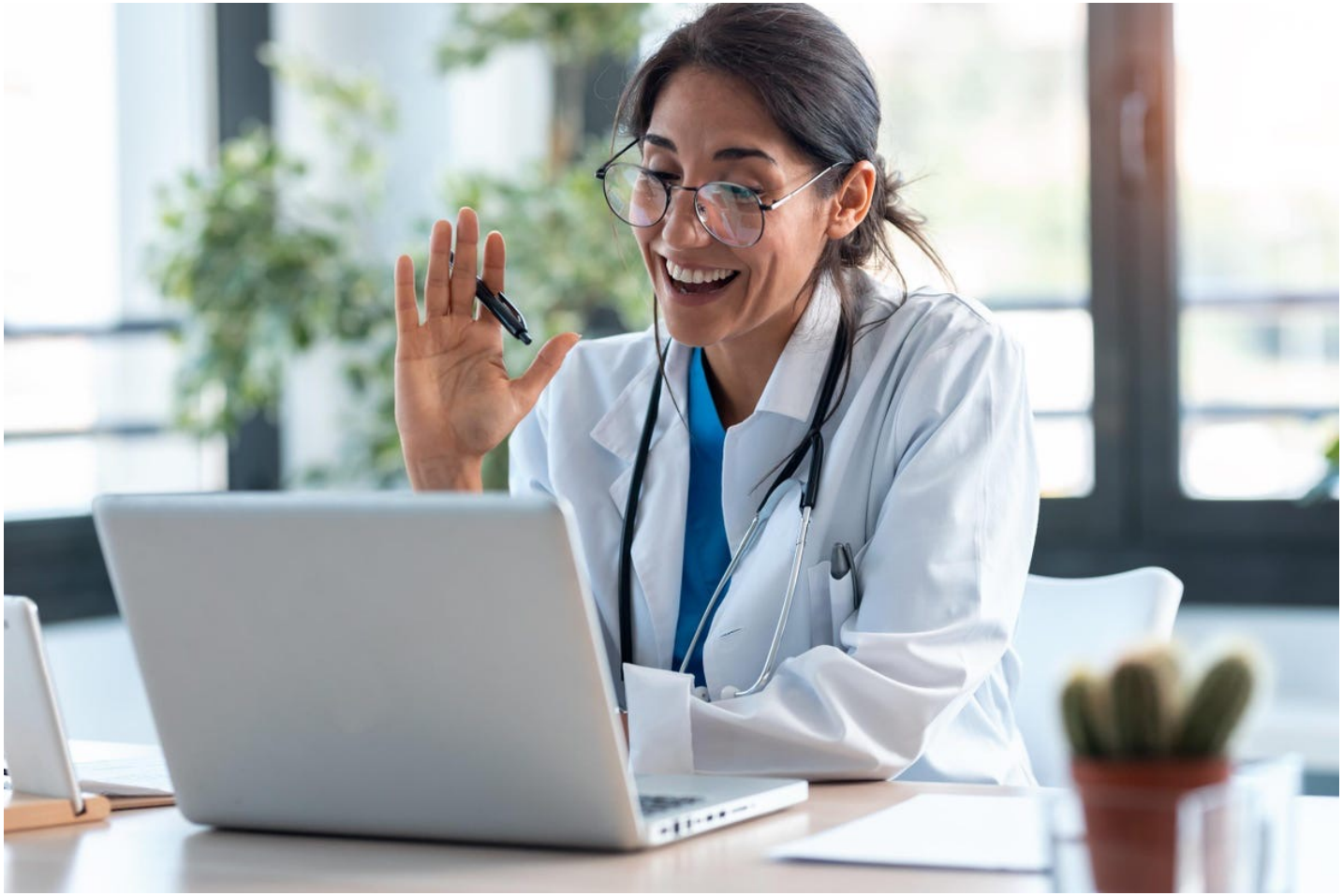
Potential for Use in MOGAD

- B cells
- Myeloid cells
  - Monocytes
  - Microglia

Phase 2 trial design

- Open label
- Recurrent MOGAD with recent disease activity
- *n* = 25
- One year of 60 mg daily dosing, no other background therapy
- Outcomes: safety, relapse prevention, MOG Ab titer

Remote Trial



Timeline

- Expected to launch in January 2023.
- Expected to read out in January 2025.

Future Preventive Therapies

- Restoring tolerance
  - BioNTech vaccine
  - 10 other companies!!

Thank you!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MDCCCCIIII
THE WORLD IS WAITING
THE CAMPAIGN FOR
HARVARD MEDICINE