Efficacy and Safety of the Selective Oral DHODH Modulator Vidofludimus Calcium (IMU-838) in Relapsing-Remitting Multiple Sclerosis:

A Randomized, Placebo-Controlled Phase 2 Trial (EMPhASIS)

2021 Virtual AAN Annual Meeting (April 17-22, 2021)

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Disclosures

RJF has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Actelion, Biogen, Celgene, EMD Serono, Genentech, Immunic, Novartis, and Teva. Dr. Fox has received research support from, or the institution he works for, has received research support from Novartis.

HW has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with AbbVie, Actelion, Alexion, Biogen, Cognomed, Biogen, F. Hoffmann-La Roche Ltd, Genzyme, Immunic, Johnson & Johnson, MedDay Pharmaceuticals, Merck Serono, Novartis, Roche Pharma AG, Sanofi-Aventis, TEVA, and WebMD Global. Dr. Wiendl has received research support from Biogen, GlaxoSmithKline GmbH, Roche Pharma AG, and Sanofi-Genzyme.

NdS has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities for Schering, Biogen-Idec, Immunic, Teva, Novartis, Sanofi-Genzyme, Roche and Merck-Serono; is on the speakers' bureaus of Biogen-Idec, Teva, Novartis, Sanofi-Genzyme, Roche, and Merck-Serono. Dr. De Stefano has received research support from or has grants or grants pending from FISM and Roche. He contributed to studies sponsored by Merck KGaA, Darmstadt, Germany.

JS has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Alexion, Biogen, Immunic, Merck, Novartis, Roche, Sanofi, Teva.

AM is employed as the Chief Medical Officer of Immunic, Inc. Dr. Muehler holds stock and/or stock options in Immunic Therapeutics which sponsored the reported clinical trial.

EMPhASIS: Phase 2 Trial of IMU-838 in RRMS (NCT03846219)

IMU-838
(Vidofludimus Calcium)

Next-generation, small-molecular DHODH inhibitor for RRMS[1]

- Optimized for human dihydroorotate dehydrogenase (DHODH) inhibition
- Lack of off-target effect on kinases
- Safety profile available from exposure to more than 800 humans

Convenient pharmacokinetic profile[2]

- Once daily oral application
- Serum half life in humans: ~ 30 hours
- Steady state trough level: 6-8 days
- Elimination from blood in most patients within 10 days without need for accelerated elimination procedure

Inclusion Criteria
RRMS With Relevant Disease Activity

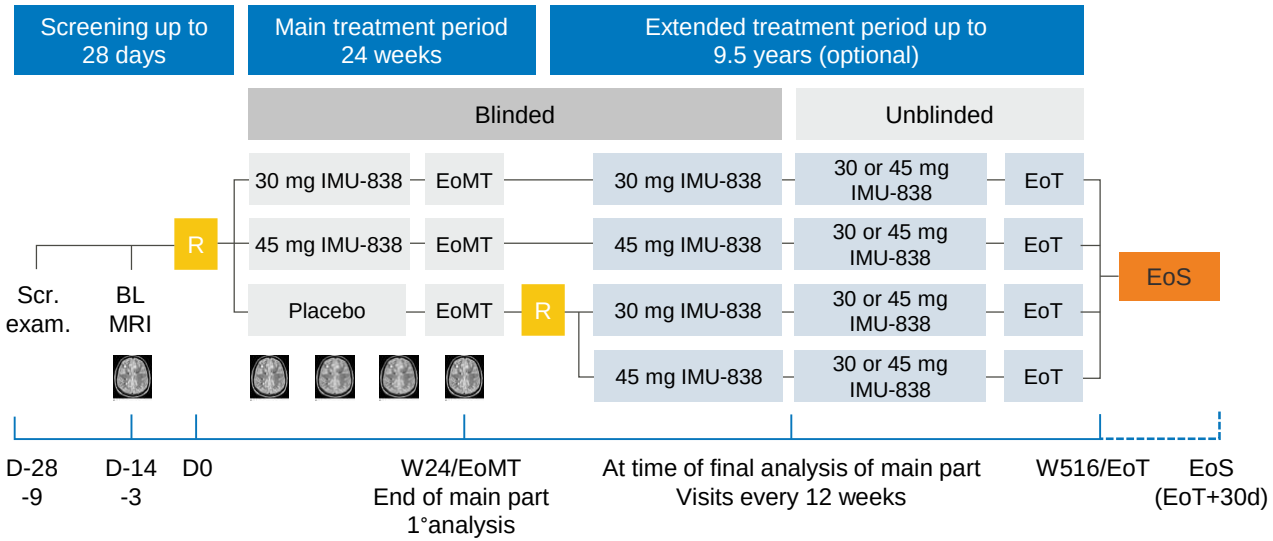
- Male or female, age ≥18 to 55 years
- RRMS diagnosis (revised McDonald criteria 2017)
- Evidence of disease activity based on relapse (1 relapse in last 12 months or 2 relapses in last 24 months) and MRI criteria (at least 1 Gd+ lesion in last 6 months before study)
- Baseline EDSS between 0 and 4.0

Double-Blind, Placebo-Controlled, Randomized, Parallel-Group Trial

- Blinded main treatment period of 24 weeks
- Extended treatment period of up to 9.5 years to observe long-term safety
- MRI every six weeks (BL, W6, W12, W18, W24)

[1] Muehler et al. Mult Scler Relat Disord. 2020;43:102129. doi:10.1016/j.msard.2020.102129
[2] Muehler et al. Eur J Drug Metab Pharmacokinet (2020). https://doi.org/10.1007/s13318-020-00623-7

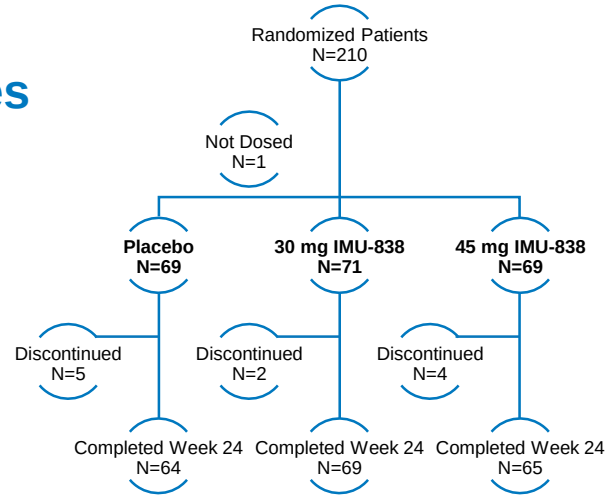
EMPhASIS Study Flow Chart



BL: baseline; exam.: examination; D: day; EoMT: end of main treatment; EoS: end of trial; EoT: end of treatment; MRI: magnetic resonance imaging; R: randomization; Scr.: screening; W: week

Patient Assignments: Low Discontinuation Rates

Treatment Discontinuation Before Week 24 (All Dosed Patients Until End of Blinded Treatment)		
Placebo	7.2%	5/69
All IMU-838	4.3%	6/140
30 mg IMU-838	2.8%	2/71
45 mg IMU-838	5.8%	4/69



Adverse events leading to treatment discontinuations

Placebo
- N=2 liver enzyme elevations*
- N=1 cervix carcinoma
- N=1 hematuria

30 mg IMU-838
- No events

45 mg IMU-838
- N=2 liver enzyme elevations*
- N=1 rash

* Protocol-required stopping rules for liver enzyme elevations were: ALT or AST >8 x ULN, or ALT or AST >5 x ULN for more than 2 weeks

Trial Met Primary and Key Secondary Endpoints

Key Study Endpoints (Efficacy Outcome):

Cumulative number of new combined unique active (CUA) magnetic resonance imaging (MRI) lesions up to Week 24

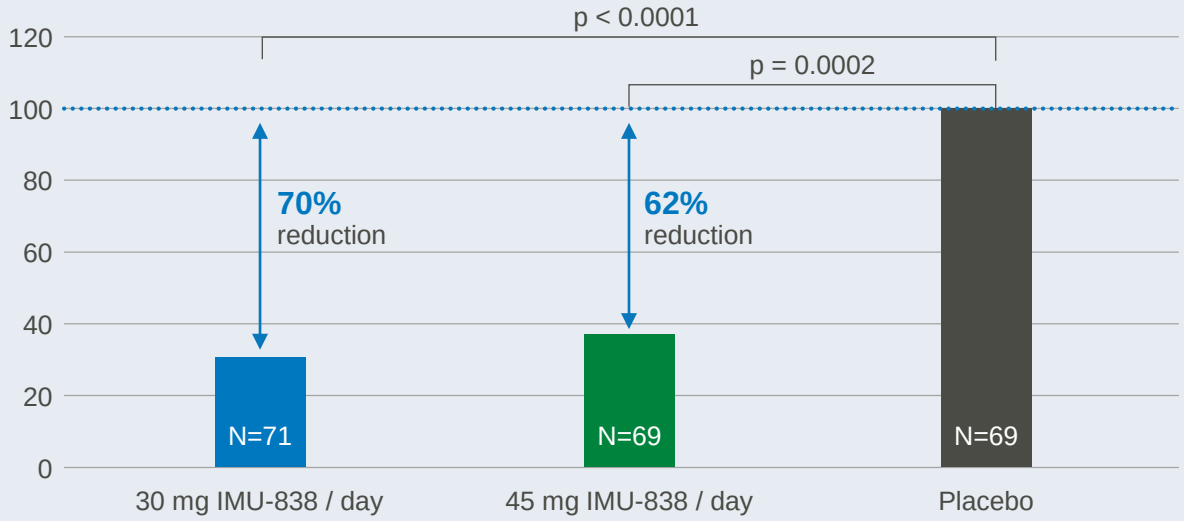
- **Primary endpoint:** Difference between **45 mg/day IMU-838** and placebo
- **Key secondary endpoint:** Difference between **30 mg/day IMU-838** and placebo

CUA MRI Lesions:

Total number of new Gadolinium-enhanced lesions on T1-weighted MRI, new or enlarged lesions on T2-weighted MRI, avoiding double counting

Key Study Endpoints

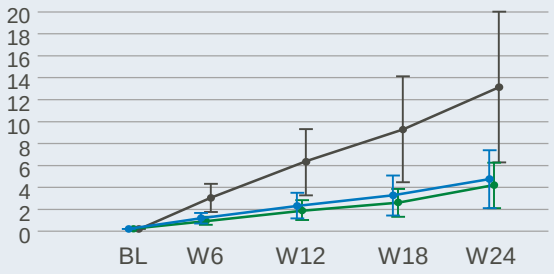
Robust Suppression of CUA MRI Lesions



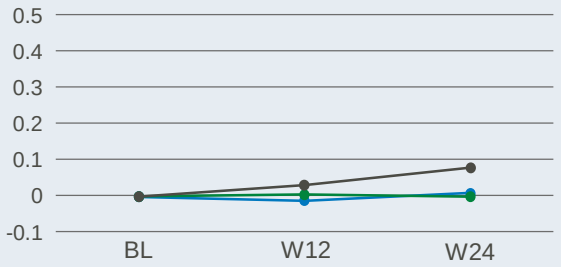
Suppression of CUA MRI lesions
IMU-838 versus Placebo over 24 weeks

Secondary Endpoints

Cumulative Number of Gd+ Lesions*



Absolute Change of EDSS from Baseline



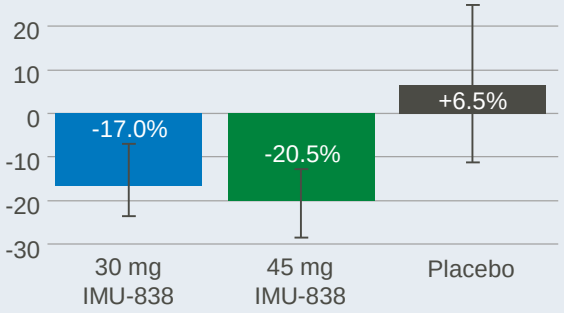
30 mg IMU-838 — 45 mg IMU-838 — Placebo

Effect on Annualized Relapse Rate (ARR)

Treatment Group	N	Adjusted Mean ARR
30 mg IMU-838	71	0.39
45 mg IMU-838	69	0.48
Placebo	69	0.53

* Displayed are adjusted mean values (and 95% confidence intervals). Estimates are adjusted for MRI field strength (1.5 or 3.0 Tesla) and baseline number of Gd+ lesions (0, >=1)
using a generalized linear model with a negative binomial distribution and a logarithmic link function. Log transformation of time from first IMP dose to date of last MRI assessment is used as offset term.

Median Percentage Change from Baseline to Week 24 in Serum Neurofilament
(Including 95% Confidence Intervals)



Robust Decrease in Serum Neurofilament Light Chain

Biomarker for Axonal Damage

Quantification of neurofilament light polypeptide (NEFL) by an electrochemiluminescent immunoassay (ECLIA) in blood serum samples

IMU-838 Was Safe and Well-Tolerated

Treatment Group	Number of TEAE	Number of Patients with TEAE
30 mg IMU-838	70	32/71 (45.1%)
45 mg IMU-838	59	28/69 (40.6%)
Placebo	62	30/69 (43.5%)

There were 3 patients with serious adverse events (SAE):
- Placebo: Squamous cell carcinoma of the cervix
- 30 mg IMU-838: open fracture, ureterolithiasis / hydronephrosis
- 45 mg IMU-838: no treatment-emergent SAE reported

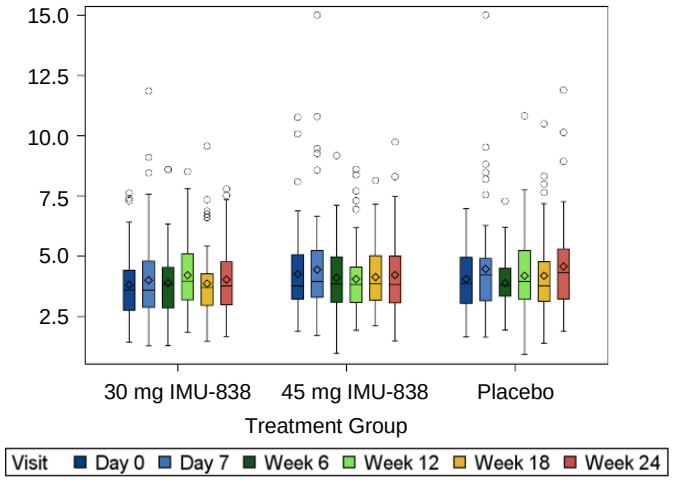
There were no on-study deaths.

TEAE by Severity	30 mg IMU-838		45 mg IMU-838		Placebo		Total	
	TEAE (N#)	Patients with TEAE, N (%)	TEAE (N#)	Patients with TEAE, N (%)	TEAE (N#)	Patients with TEAE, N (%)	TEAE (N#)	Patients with TEAE, N (%)
Mild	50	29 (40.8)	38	21 (30.4)	46	23 (33.3)	134	73 (34.9)
Moderate	19	11 (15.5)	21	16 (23.2)	14	8 (11.6)	54	35 (16.7)
Severe	0	0 (0)	0	0 (0)	2	1* (1.4)	2	1 (0.5)
Total	69	32 (45.1)	59	28 (40.6)	62	30 (43.5)	190	90 (43.1)

Renal, Hepatic, Hematology Safety

Liver Enzyme Elevations	30 mg IMU-838	45 mg IMU-838	Placebo
# of Patients Evaluated	71	69	69
ALT or AST >5xULN	1 (1.4%)	3 (4.3%)	2 (2.9%)
ALT or AST >10xULN	0 (0%)	1 (1.4%)	1 (1.4%)
ALT or AST >15xULN	0 (0%)	0 (0%)	0 (0%)

No Generalized Effect on Neutrophils Count



Renal Events	30 mg IMU-838		45 mg IMU-838		Placebo		Total	
	TEAE (N#)	Patients with TEAE, N (%)	TEAE (N#)	Patients with TEAE, N (%)	TEAE (N#)	Patients with TEAE, N (%)	TEAE (N#)	Patients with TEAE, N (%)
Blood Creatinine Increased	1	1 (1.4)	0	0 (0.0)	0	0 (0.0)	1	1 (0.5)
Chromaturia	0	0 (0.0)	1	1 (1.4)	0	0 (0.0)	1	1 (0.5)
Hematuria	0	0 (0.0)	0	0 (0.0)	1	1 (1.4)	1	1 (0.5)
Hydronephrosis	1	1 (1.4)	0	0 (0.0)	0	0 (0.0)	1	1 (0.5)
Ureterolithiasis	1	1 (1.4)	0	0 (0.0)	0	0 (0.0)	1	1 (0.5)
Total	4	**2** (2.8)	1	**1** (1.4)	1	**1** (1.4)	6	**4** (1.9)

TEAE: treatment-emergent adverse events; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal
TEAE are displayed by intensity.
*One patient on placebo treatment experienced the severe adverse events of leukopenia and neutropenia.

Conclusions

Discussion Monday, April 19, 12:30p EDT:
https://meet.ccf.org/foxr/199Y6GV9

Efficacy

- Primary and key secondary endpoints met: 62-70% reduction in combined unique active MRI lesions
- All other secondary endpoints consistently favorable to IMU-838, although no formal statistical testing was planned for secondary endpoints
- MRI lesion suppression by IMU-838 compares favorably to other first-line and oral medications in relapsing multiple sclerosis

Safety

- Consistent with prior studies in other patient populations, IMU-838 was safe and well-tolerated
  - Safety profile is comparable to the placebo group
- Very low rate of treatment discontinuations
  - Compares favorably to other multiple sclerosis therapies
- Favorable safety profile
  - No increase in liver or renal events
  - No hepatotoxicity signal

A phase 3 program is being planned
and expected to start in the **second half of 2021**