# Safety and tolerability of IMU-838, a next-generation DHODH inhibitor in EMPhASIS: a randomized, placebo-controlled phase 2 trial in relapsing MS

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### 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 reached in 6-8 days
- Elimination from blood in most patients within 10 days without need for accelerated elimination procedure

### Study population
- 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)

### Objective
To compare safety and tolerability of IMU-838 in the EMPhASIS trial with corresponding parameters from the placebo-controlled phase 2 trial of the first-generation DHODH inhibitor teriflunomide in MS (O'Connor, 2006)[3].

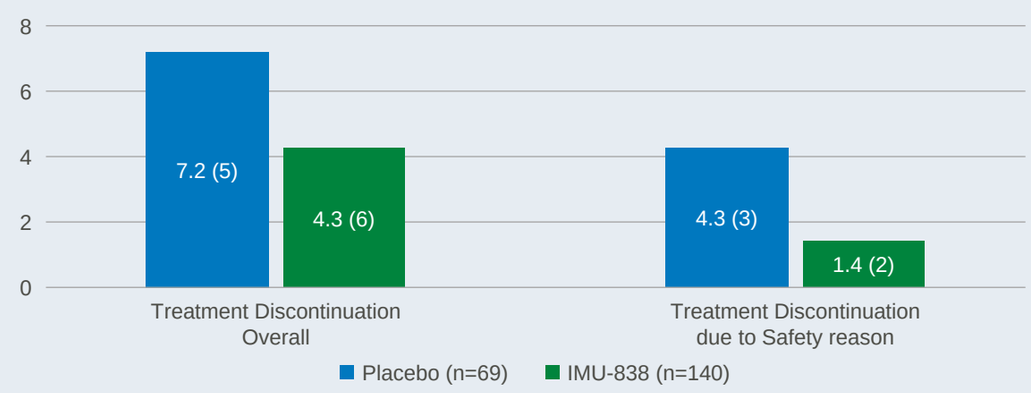
### Methods
Discontinuation rates and treatment emergent adverse events (TEAE) of the two independent clinical trials are presented. These were all adverse events reported during the main treatment period, starting from day 1 up to completion at Week 24 in the clinical study with IMU-838 and up to completion at Week 36 in the clinical study with teriflunomide.

### Efficacy
IMU-838 met the primary outcome parameter of suppressing the number of cumulative unique active (CUA) lesions on brain MRI, showing a relative reduction (RR) of 70% for 30 mg and 62% for 45 mg vs. placebo.

## Results

**Treatment discontinuations rates in IMU-838 arm were numerically less frequent than in the placebo arm. Additionally, IMU-838 discontinuation rates compare favorably to Teriflunomide data from it's Phase 2 study in RMS (O'Connor, 2006)[3]. This was shown even more significant for discontinuations due to safety reasons.**

**IMU-838 Phase 2 study in RMS, 24-weeks** [% (N)]




**Teriflunomide Phase 2 Study in RMS, 36 weeks** (O'Connor, 2006)[3]

**Treatment discontinuations** [% (N)]

| Overall | | Due to safety | |
|---|---|---|---|
| **Placebo** (n=61) | **Teriflunomide** (n=118) | **Placebo** (n=61) | **Teriflunomide** (n=118) |
| 6.6 (4) | 11.0 (13) | 6.6 (4) | 8.5 (10) |

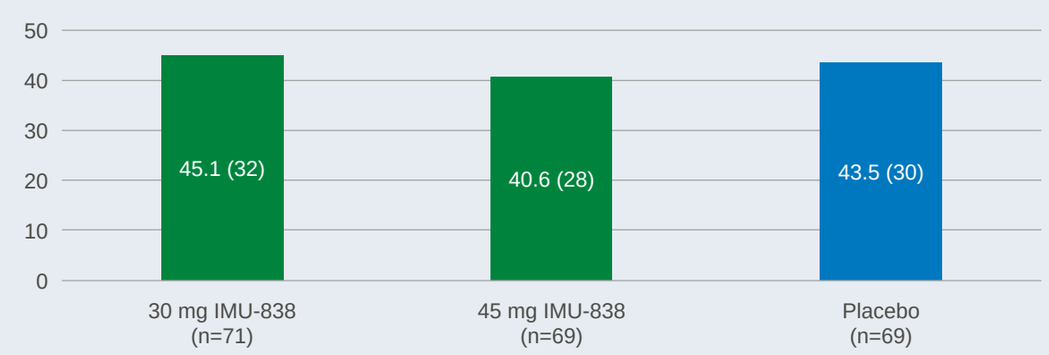
**IMU-838 showed lower incidence of treatment emergent adverse events typical for DHODH inhibitors than teriflunomide.**

**Patients with TEAE** [% (N)]

| | IMU-838 Phase 2 study in RMS, 24 weeks | | Teriflunomide Phase 2 Study in RMS, 36 weeks (O'Connor, 2006)[3] | |
|---|---|---|---|---|
| **TEAE** | **Placebo** (n=69) | **IMU-838 Total** (n=140) | **Placebo** (n=61) | **Teriflunomide Total** (n=118) |
| Nasopharyngitis | 4.3 (3) | 5.7 (8) | 16 (10) | 22.0 (26) |
| Resp./Upper Respiratory Tract Inf. (total) | 8.6 (6) | 2.8 (4) | NA | NA |
| • Respiratory tract infections | | 1.4 (2) | NA | NA |
| • Upper Respiratory Tract Inf. | 4.3 (3) | 1.4 (2) | 21 (13) | 20.3 (24) |
| Headache | 5.8 (4) | 5.0 (7) | 26 (16) | 22.8 (27) |
| Hepatic enzyme/ALT elevation | 1.4 (1) | 2.8 (4) | NA | NA |
| ALT elevation | 4.3 (3) | 0.7 (1) | 10 (6) | 14.4 (17) |
| Nausea | 1.4 (1) | 2.1 (3) | 5 (3) | 14.4 (17) |
| Diarrhea | 0 | 0 | 5 (3) | 10.1 (12) |
| Alopecia | 0 | 2.8 (4) | 10 (6) | 16.9 (20) |

**Occurrence of TEAEs was similar in both IMU-838 and in the placebo arms.**

**Patients with TEAE** [% (N)]




**Serious TEAEs occurred only in two patients treated with IMU-838.**

**Patients with Serious TEAEs** [% (N)]

| Placebo (n=69) | IMU-838 (n=140) | Placebo (n=61) | Teriflunomide (n=118) |
|---|---|---|---|
| 1.4 (1) | 1.4 (2) | 11.5 (7) | 10.2 (12) |

**Types of Serious TEAEs**
- Open fracture
- Ureterolithiasis

**Types of Serious TEAEs**
- Elevated liver enzymes
- Hepatic dysfunction
- Neutropenia
- Rhabdomyolysis
- Trigeminal neuralgia

## Conclusion

In this phase 2 study of IMU-838 in RMS, patients treated with IMU-838 discontinued treatment less frequently and had similar rates of adverse events, as patients treated with placebo. In addition, IMU-838 data from this study compare favorably with results of a separate phase 2 study with teriflunomide. The higher selectivity and lower off-target inhibition of protein kinases of IMU-838 may explain the potentially advantageous safety and tolerability profile.


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
3 O'Connor et al. Neurology 2006;66:894-900. doi: 10.1212/01.wnl.0000203121.04509.31.