# Assessment of dose-dependency of anti-inflammatory and neuroprotective efficacy variables and biomarkers for vidofludimus calcium in EMPhASIS:

## A randomized, placebo- controlled phase 2 trial in relapsing-remitting multiple sclerosis

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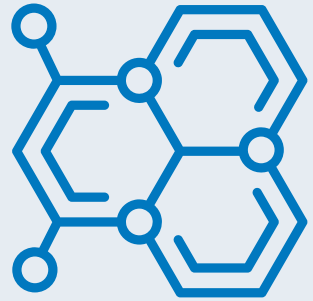
# Disclosures

- RJF: reports personal fees from AB Science, Biogen, Celgene, EMD Serono, Genentech, Genzyme, Immunic AG, Janssen Novartis, Sanofi, and TG Therapeutics; clinical trial contracts from Biogen, Novartis, and Sanofi.
- HW: reports grants and personal fees from AbbVie, Biogen, Merck Serono, and Sanofi Genzyme; personal fees from Actelion, Alexion, Evgen, F. Hoffmann-La Roche, Gemeinnützige Hertie-Stiftung, Immunic, Lundbeck, MedDay Pharmaceuticals, Novartis, Roche Pharma, AG, Teva, and WebMD Global; and grants from Deutsche Forschungsgesellschaft (DFG), Else Kröner Fresenius Foundation, European Union, Fresenius Foundation, German Ministry for Education and Research (BMBF), GlaxoSmithKline, Hertie Foundation, Interdisciplinary Center for Clinical Studies (IZKF) Muenster, NRW Ministry of Education and Research, PML Consortium, RE Children's Foundation, and Swiss MS Society, outside the submitted work.
- CW: is a partner at Lycalis sprl and reports compensation for his organisation for consulting from BMS, Celgene, Desitin, Immunic, Merck KGaA, Novartis, Roche, Synthon, Teva, and Viatris; and for speaking from Synthon and Viatris.
- NdS: has received honoraria from Biogen- Idec, Genzyme, Immunic, Merck, Novartis, Roche, Celgene and Teva for consulting services, speaking, and travel support. He serves on advisory boards for Merck, Novartis, Biogen-Idec, Immunic, Roche, and Genzyme, and he has received research grant support from the Italian MS Society.
- JS: received honoraria for participation in advisory boards, consultancy and lecturing from Biogen, BMS, Immunic, Merck, Novartis, Roche and Sanofi.
- VG: reports grants/personal fees from Medpace, PPD, PRA Health Sciences, PSI, Roche, Sanofi, and Verum.
- KR: is the president elect of the Polish Neurological Society.
- PSB: nothing to disclose.
- NT: nothing to disclose.
- IS: nothing to disclose.
- AM: is a shareholder and employee of trial sponsor, and a holder of patents for the drug under investigation.

# **IMU-838** (Vidofludimus Calcium)

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

- Optimized for human DHODH inhibition
- Lack of off-target effect on kinases
- Safety profile obtained from exposure to **1100+** 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

[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

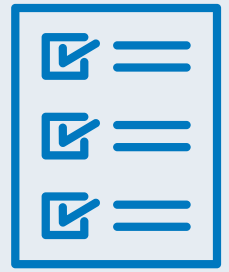
# EMPhASIS: Phase 2 Study Overview

## Included population: RRMS with relevant disease activity

- Male or female ( 18 ≤ age ≤ 55)
- 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: 0 ≤ EDSS ≤ 4.0
- Standard laboratory and corticosteroid use exclusions

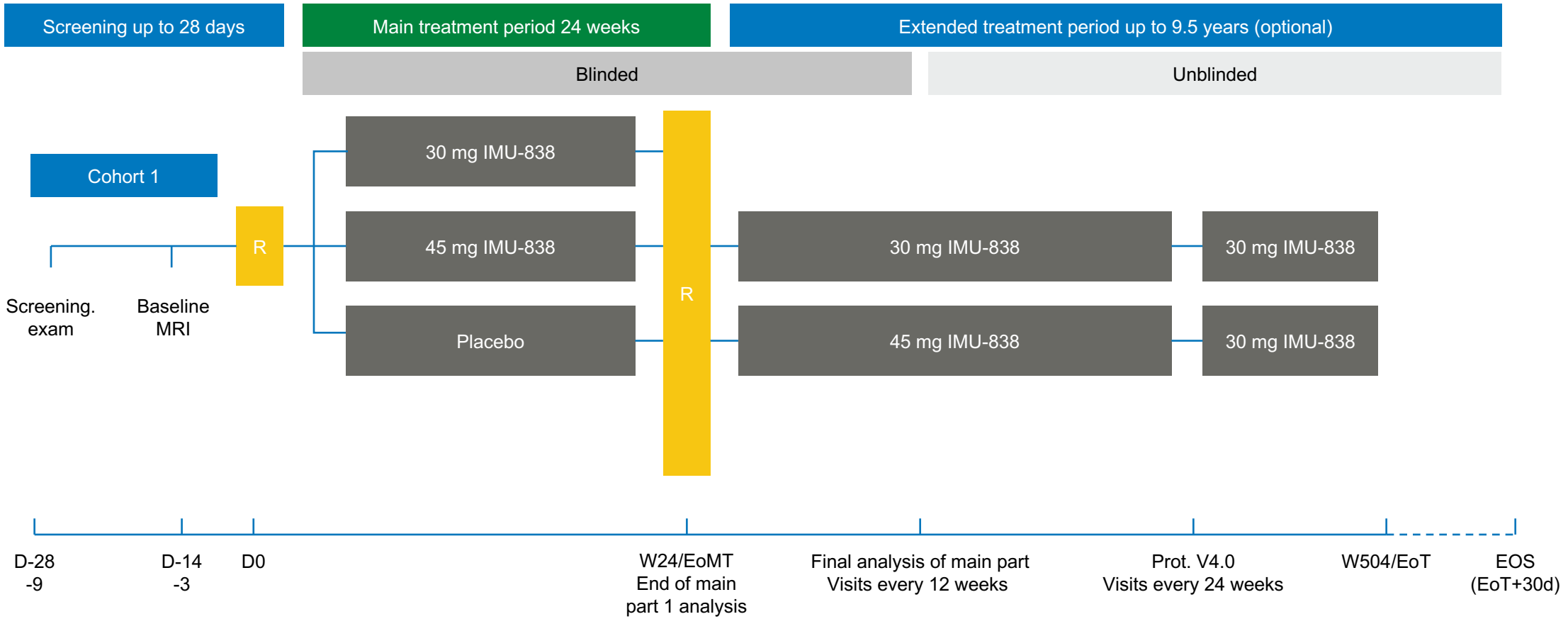
## Study objectives

- Primary objective: efficacy assessed on MRI by numbers of CUA and Gad+ lesions
- Pharmacokinetics and determination of the lowest effective dose (Cohort 2)
- Safety and tolerability of different doses of vidofludimus calcium



# EMPhASIS: Phase 2 Trial Design in RRMS

## Trial Flow Chart



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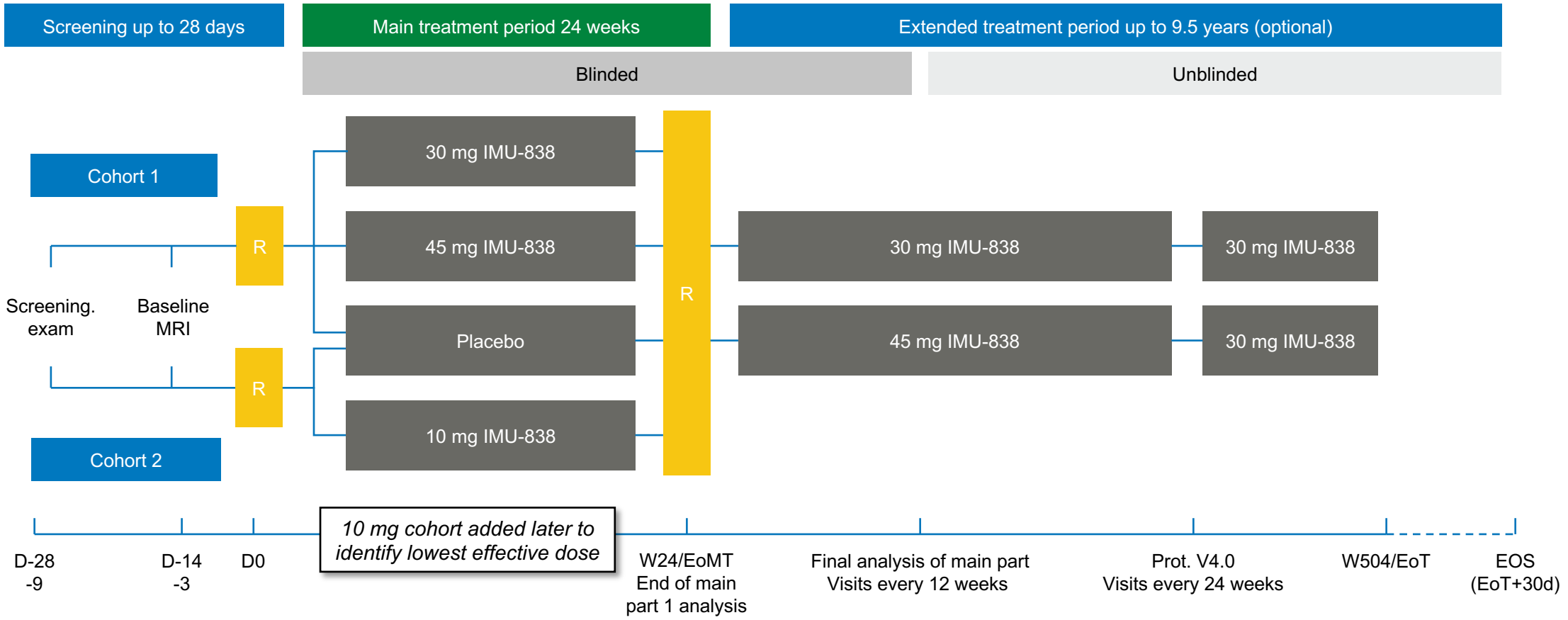
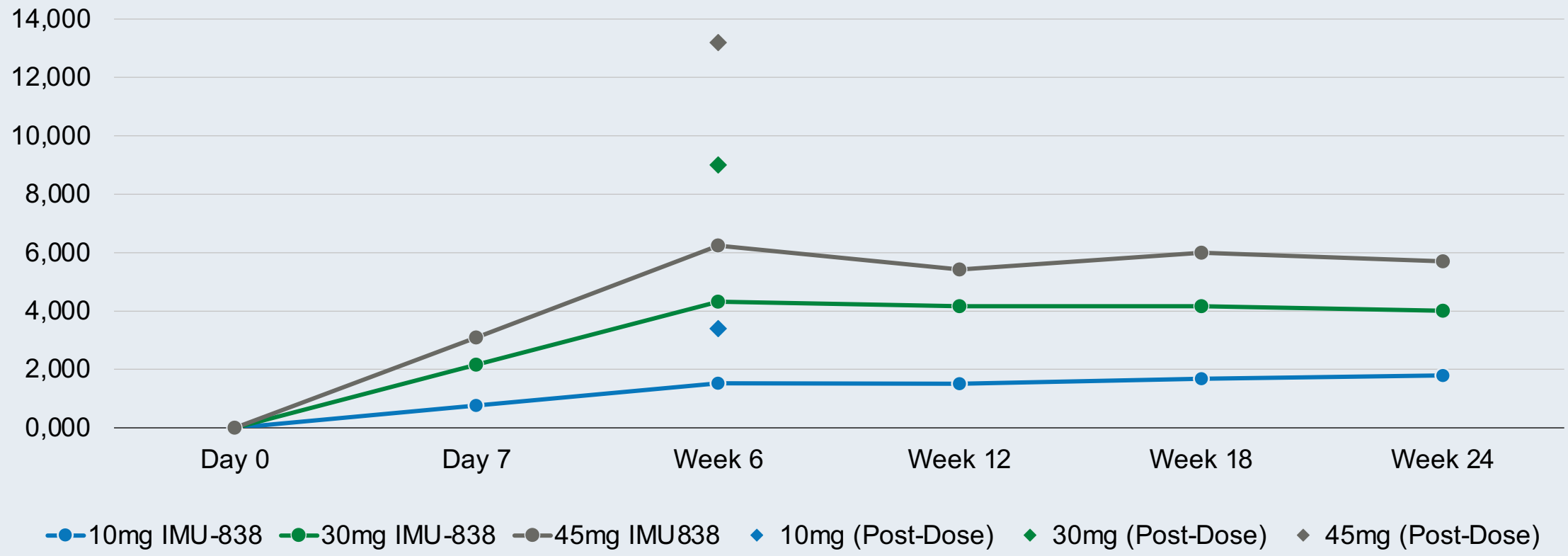


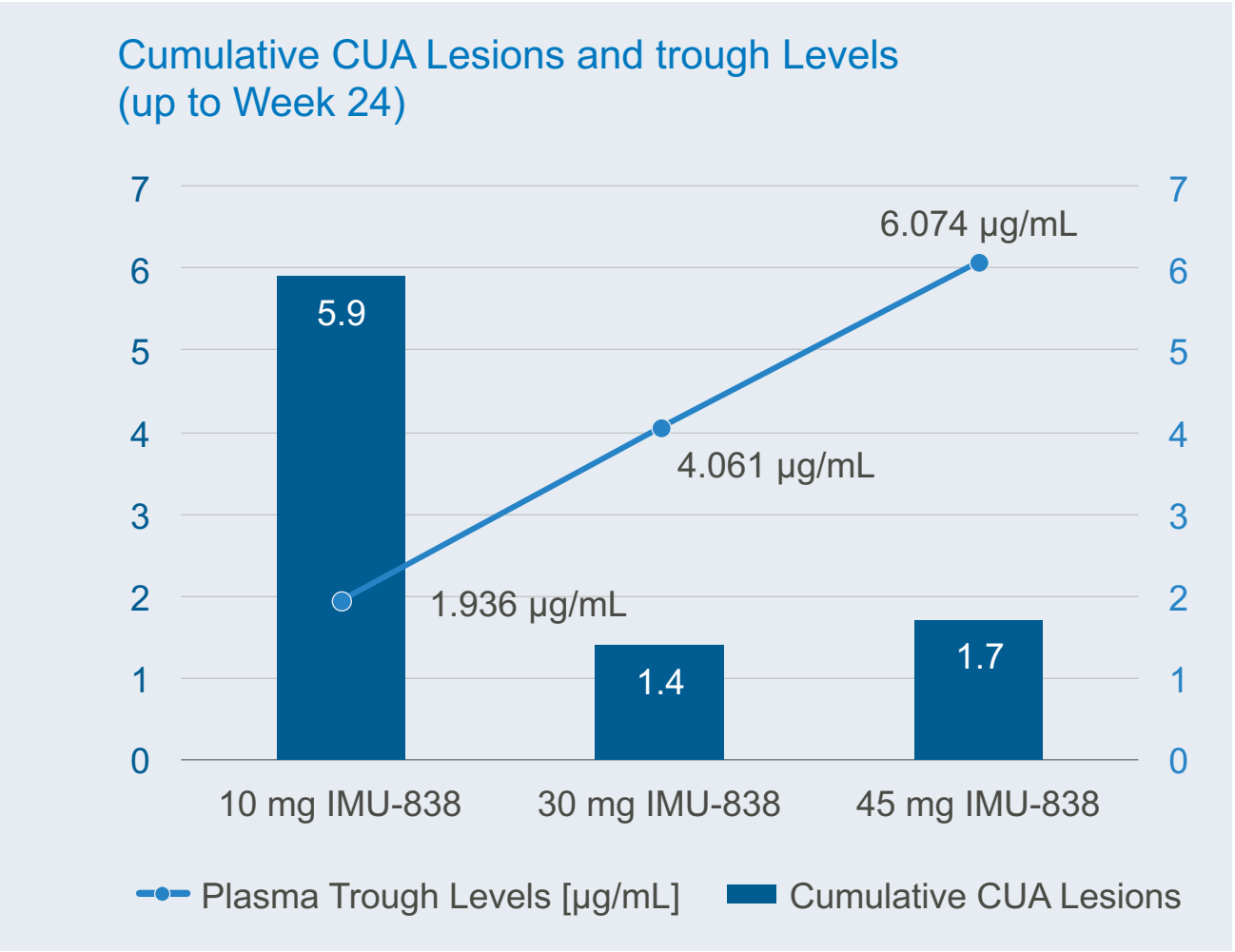
# Vidofludimus

## Plasma Trough and Peak Levels (µg/mL) (up to Week 24)




Safety analysis set C1/C2 ($N_{10}$ =47, $N_{30}$ =71, $N_{45}$ =69, $N_{PBO}$ =81)
The mean trough value is indicated by an oval marker, the mean peak post-dose value at week 6 is displayed by a diamond.

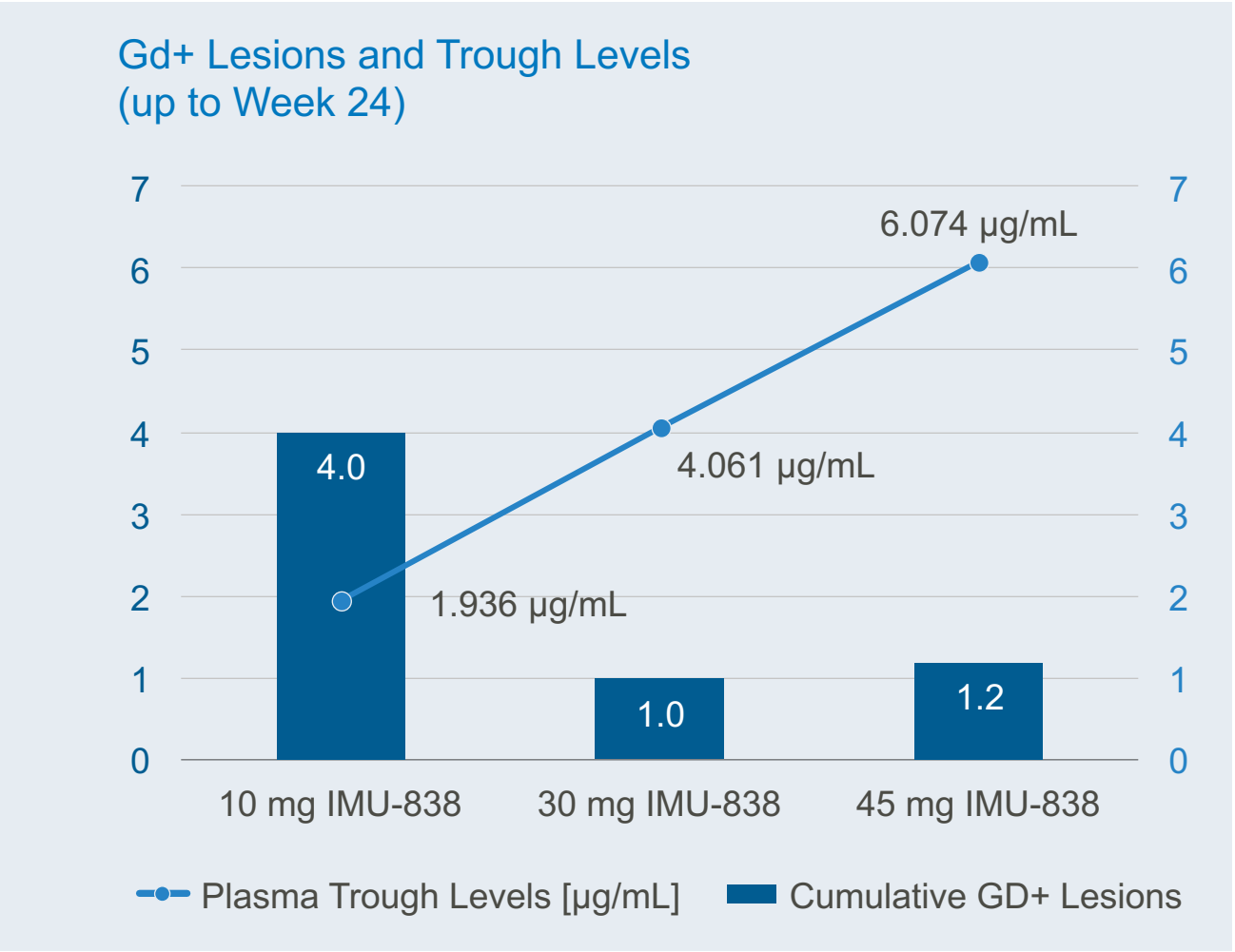
# Relationship Between Trough Levels of Vidofludimus and Number of Cumulative CUA Lesions at Week 24




| Treatment Group | Adjusted Mean | Percentage Change |
|---|---|---|
| Placebo | 5.8 | (ref) |
| 10 mg IMU-838 | 5.9 | +2% |
| 30 mg IMU-838 | 1.4 | -76% |
| 45 mg IMU-838 | 1.7 | -71% |

Cumulative CUA: cumulative combined unique active

# Relationship Between Trough Levels of Vidofludimus and Number of Gd+ Lesions at Week 24

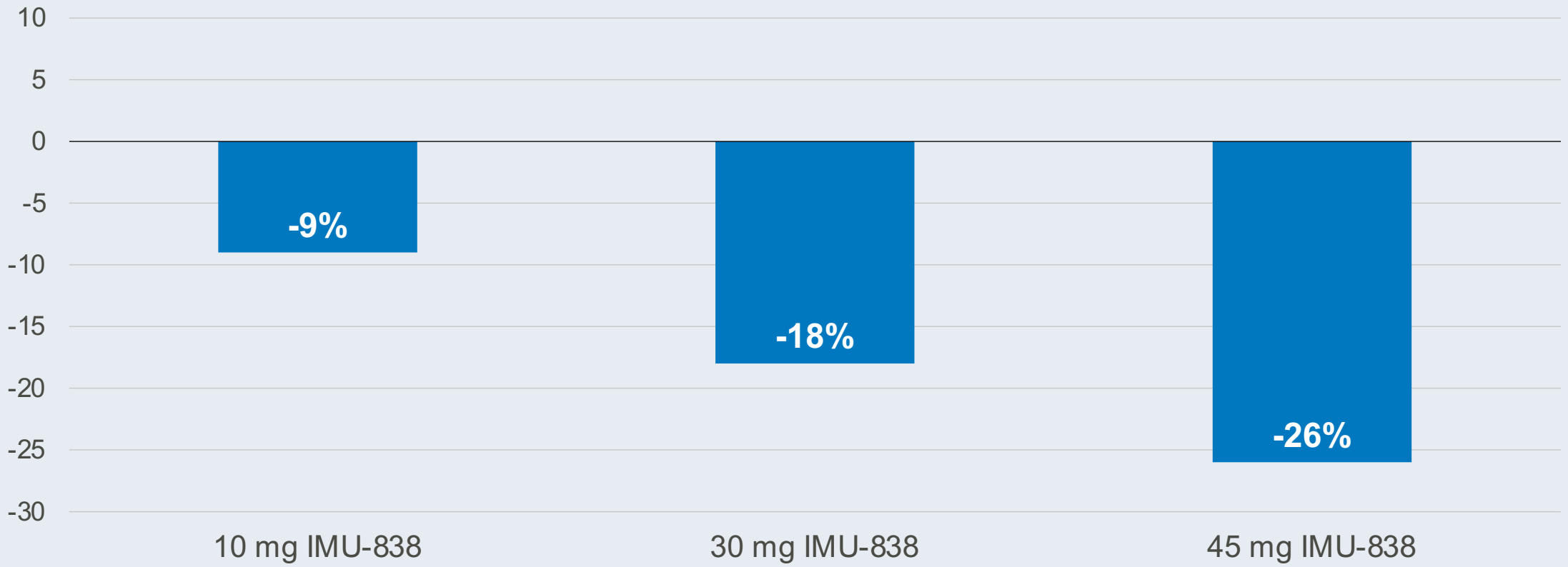



| Treatment Group | Adjusted Mean | Percentage Change |
|---|---|---|
| Placebo | 4.6 | (ref) |
| 10 mg IMU-838 | 4.0 | -13% |
| 30 mg IMU-838 | 1.0 | -78% |
| 45 mg IMU-838 | 1.2 | -74% |

Gd+: gadolinium-enhancing

# Dose-dependent reduction of NfL

## Median % Change of Serum Neurofilament from Baseline Compared to Placebo




Displayed are median values of differences between percentage change of serum neurofilament light chain concentration (Hodges-Lehmann estimation), treatment vs. placebo, combined data for Cohort 1 and 2 patients; NfL: neurofilament light chain

# No Safety signal (dose-dependent or otherwise)

| Serious Adverse Events (SAEs) | Placebo (N=81) | 10 mg IMU-838 (N=47) | 30 mg IMU-838 (N=71) | 45 mg IMU-838 (N=69) |
|---|---|---|---|---|
| Number of patients | 1 | 0 | 2 | 0 |
| Number of events leading to discontinuations | 1 | 0 | 2 | 0 |
| Types of SAEs | Squamous cell carcinoma of the cervix | None | Open fracture<br>Ureterolithiasis/tubulo-interstitial nephritis | None |

| All Adverse Events | Placebo (N=81) | 10 mg IMU-838 (N=47) | 30 mg IMU-838 (N=71) | 45 mg IMU-838 (N=69) |
|---|---|---|---|---|
| Number of patients (%) | 35 (43.5) | 11 (23.4) | 32 (45.1) | 28 (40.6) |
| Number of Adverse Events | 68 | 12 | 69 | 59 |

| Infections and Infestations | Placebo (N=81) | 10 mg IMU-838 (N=47) | 30 mg IMU-838 (N=71) | 45 mg IMU-838 (N=69) |
|---|---|---|---|---|
| Number of patients (%) | 25 (24.7) | 8 (17.0) | 13 (18.3) | 16 (23.2) |

| Liver Enzyme Elevations | Placebo (N=81) | 10 mg IMU-838 (N=47) | 30 mg IMU-838 (N=71) | 45 mg IMU-838 (N=69) |
|---|---|---|---|---|
| ALT or AST >5xULN | 2 (2.5%) | 0 (0%) | 1 (1.4%) | 3 (4.3%) |

# Conclusion

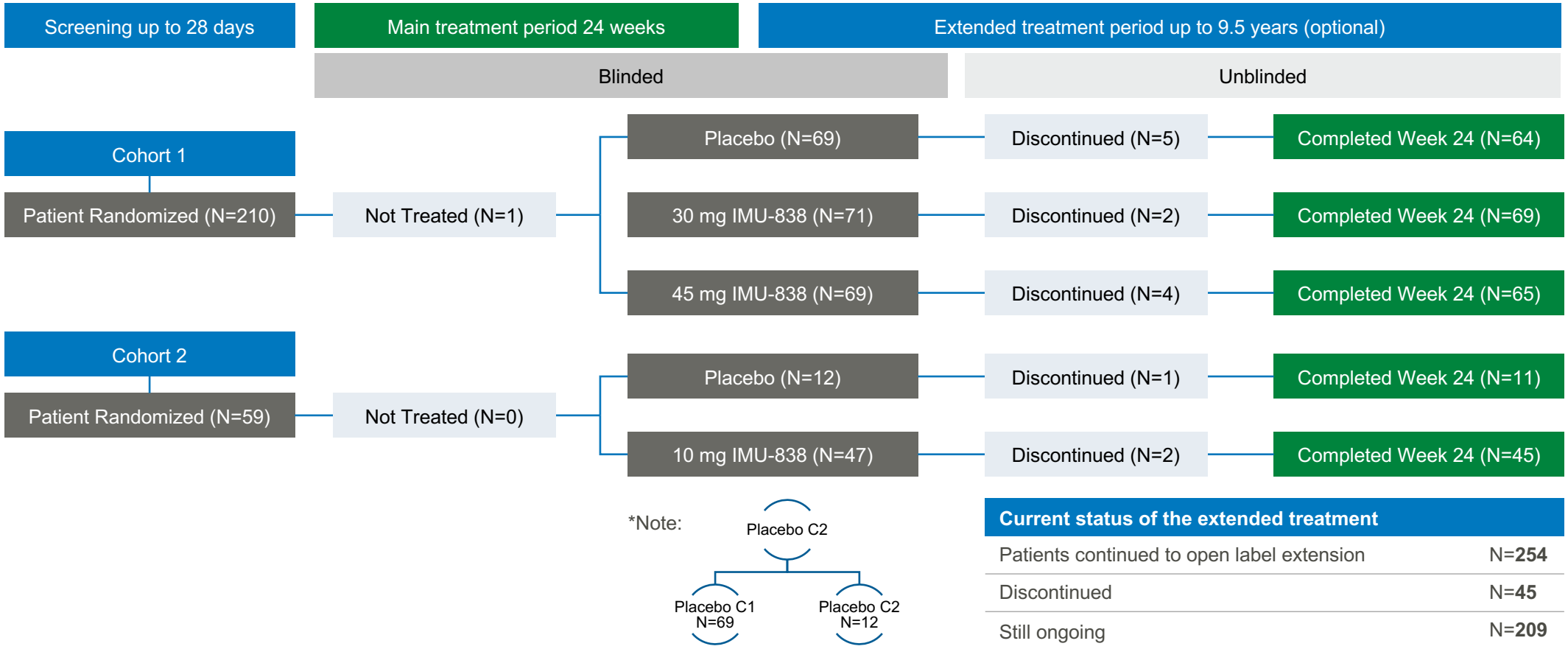
- Doses of 30 and 45 mg of vidofludimus calcium showed compelling **anti-inflammatory effects** (with 65 – 78% reduction in CUA and Gd+ lesions) and other signs of clinical activity
- A dose-dependent neuroprotective effect of vidofludimus calcium was shown on serum NfL in the 10 to 45 mg dose groups
- The Cohort 1 and 2 results confirm the 30 mg dose as the lowest effective dose and as the appropriate Phase 3 dose for evaluation of relapsing MS patients
- The results indicate favorable safety and tolerability profile of vidofludimus calcium

# Thank you.

# Back-up slides

# EMPhASIS: Phase 2 Trial in RRMS

## Patient Disposition in Main Period




| Current status of the extended treatment | |
|---|---|
| Patients continued to open label extension | N=**254** |
| Discontinued | N=**45** |
| Still ongoing | N=**209** |

In order to provide sufficient data points in the placebo arm, Cohort 1 placebo patients from the same sites that contributed to the Cohort 2 analysis and who were investigated using 1.5 Tesla MRI examinations were allowed to enrich the Cohort 2 placebo arm for all MRI-based analyses. In addition, summary data from Cohort 1 30 mg/day and 45 mg/day data are shown as comparison to Cohort 2 data from 10 mg/day IMU-838. The Cohort 1 data for 30 and 45 mg IMU-838 includes only Week 24 MRI data performed at 1.5 Tesla field strength.

# Discontinuations

## Treatment Discontinuation before Week 24 (all dosed patients until end of blinded treatment)

N (%)

| Placebo (N=81) | 10 mg IMU-838 (N=47) | 30 mg IMU-838 (N=71) | 45 mg IMU-838 (N=69) |
|---|---|---|---|
| **6** (7.4) | **2** (4.3) | **2** (2.8) | **4** (5.8) |

## Reason for discontinuation treatment

- Liver enzyme elevations (N=2)
- Cervix carcinoma (N=1)
- Haemarturia (N=1)
- Other reason not related to IMP or AE (N=2)

- Other reason not related to IMP or AE (N=2)

- Other reason not related to IMP or AE (N=2)

- Liver enzyme elevations (N=2)
- Rash (N=1)
- Other reason not related to IMP or AE (N=1)