Vidofludimus Calcium

Development Program in Relapsing Multiple Sclerosis

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Immunic THERAPEUTICS

EMPhASIS: Completed Phase 2 Trial in Relapsing-Remitting MS

NCT03846219

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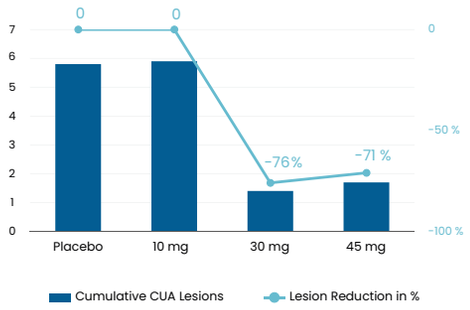
Double-Blind, Placebo-Controlled, Randomized, Parallel-Group Trial

- Blinded main treatment period of 24 weeks
- Cohort 1: 30 and 45 mg or placebo QD
- Cohort 2: 10 mg or placebo QD
- Randomized 268 patients in 36 centers across four European countries
- Extended treatment period of up to 9.5 years to observe long-term safety is ongoing

EMPhASIS: Reduction of MRI Lesion Activity [1,2]

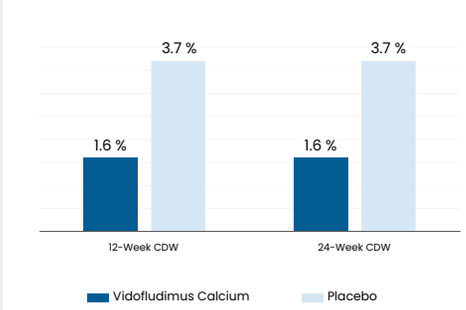
Cumulative CUA Lesions up to Week 24



Primary and key secondary endpoints of cumulative number of new CUA lesions up to week 24 met with high statistical significance (primary 45 mg vs. placebo: p = 0.0002 / key secondary 30 mg vs. placebo: p < 0.0001)

Signal in Preventing CDW Event [1,2]

Percentage of Patients With CDW Event



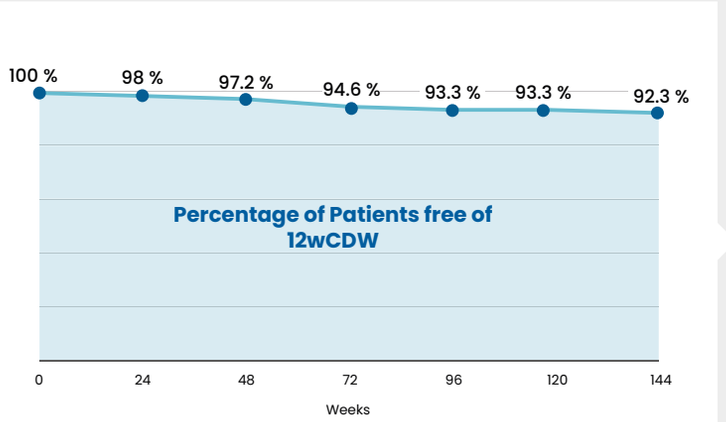
- Signal in preventing 12-week and 24-week confirmed disability worsening events as compared to placebo
- Confirmatory data are being sought in the Phase 3 ENSURE clinical program

EMPhASIS: Vidofludimus Calcium Well-Tolerated With Adverse Events Rates Similar to Placebo [1,2]

Safety	Placebo (n=81)	Vidofludimus Calcium, any dose (n=187)[a]
Treatment-emergent adverse event[b]	35 (43 %)	71 (37 %)
Serious adverse events	1 (1 %)	2 (1 %)
Treatment-emergent adverse event leading to treatment discontinuation	4 (5 %)	3 (2 %)
Liver enzyme elevations (ALT or AST > 5 x upper limit of normal)	2 (3 %)	4 (2 %)
Infections	20 (25 %)	37 (20 %)
Renal events	2 (2 %)	5 (3 %)

[a] consist of patients receiving 10 mg, 30mg, 45 mg of vidofludimus calcium; [b] treatment-emergent adverse were defined as any event not present before the first dose of placebo or vidofludimus calcium or any event already present that worsened in either intensity or frequency following treatment; ALT: alanine aminotransferase, AST: aspartate aminotransferase

Open-Label Extension: 92.3 % of Patients Free of 12-Week CDW at Week 144[3]



- A total of 29 CDW events were confirmed at 12-weeks following the trigger event up to Week 144.
- Of these, 13 (44.8%) were defined as relapse-associated worsening and 4 (13.8%) were progression independent of relapse activity.
- Low discontinuations rate with 196 patients of 254 reached 144 weeks of OLE treatment.

MS: multiple sclerosis; QD: quaque die = once-daily; As Cohort 2 only allowed MRI machines of 1.5T, pooled data of Cohorts 1 & 2 only include patients that were evaluated at MRI field strength of 1.5 Tesla. Modified full analysis set C1/C2 (N10 = 47, N30 = 65, N45 = 66, NPBO C1 = 59, NPBO C2 = 12). Data displayed are as adjusted mean values. RRMS: relapsing-remitting multiple sclerosis; MRI: magnetic resonance imaging; CUA: cumulative unique active. CDW: confirmed disability worsening; EDSS: Expanded Disability Status Scale. Only disability worsenings with a trigger point during the 24-wek blinded treatment period are considered. The EDSS increases during the blinded treatment phase were subsequently confirmed during open-label extension phase of the trial. Patients at risk in this analysis are 187 for vidofludimus calcium (pooling 10, 30 and 45 mg data) and 81 for placebo. The trigger event is an EDSS progression defined as an increase in the EDSS compared to Baseline of at least 1.5 points if Baseline EDSS = 0, of at least 1.0 points if Baseline EDSS of 1-5, or of at least 0.5 points if Baseline EDSS ≥ 5.5
12-week CDW: The confirmation event is at least 77 days after the trigger event. At the confirmation event and each assessment between trigger and possible confirmation event, EDSS must be at least as high as at the trigger event.
24-week CDW is are defined analogously, the only difference being the time interval between trigger event and confirmation visit, which is at least 161 days. Full analysis set pooled cohorts 1&2 (N10 = 47, N30 = 71, N45 = 69, NPBO C1 = 69, NPBO C2 = 12)
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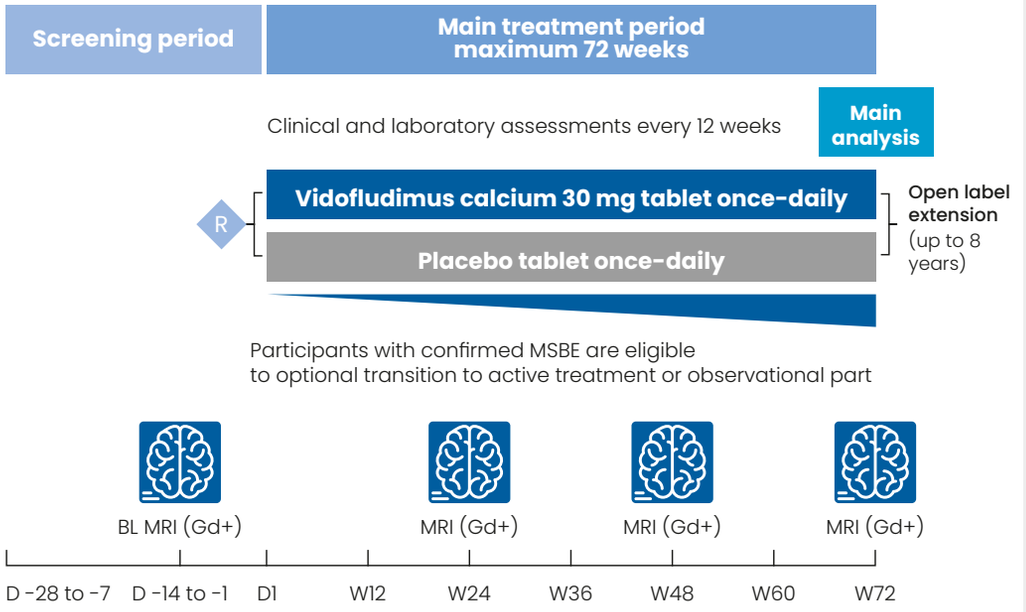
EMPhASIS: Summary Phase 2 Trial in Relapsing-Remitting MS [1,2]

- Treatment with vidofludimus calcium led to a reduction in new MRI lesions in patients with RRMS.
- Vidofludimus calcium was found to be safe and well-tolerated. The incidences of liver enzyme elevations and infections were similar to placebo.
- Assessment in longer, larger trials is justified.

ENSURE Program

Two Phase 3 Clinical Trials Comparing Vidofludimus Calcium With Placebo in Adult Participants With Relapsing Multiple Sclerosis (NCT05134441 & NCT05201638)

PRIMARY OBJECTIVE	To evaluate efficacy of vidofludimus calcium versus placebo in delaying the occurrence of relapses based on time to first relapse.
SECONDARY OBJECTIVE	To evaluate efficacy of vidofludimus calcium versus placebo on disability progression.
STATUS	Fully enrolled, ENSURE-1: 1121 patients, ENSURE-2: 1100 patients.



MSBE: MS breakthrough event; BL: baseline; MRI: magnetic resonance imaging; Gd+: gadolinium-enhancing; R: randomization; D: day; W: week
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Primary Endpoint

- Time to first relapse, occurred after the start of study treatment administration and before the end of the double-blind period.

Secondary Clinical and MRI Endpoints

- Time to 12-week confirmed disability worsening based on expanded disability status scale (EDSS) during the double-blind period.
- Changes in total volume of new T2-lesions from baseline MRI until week 24 MRI.
- Cognitive performance measured by confirmed clinically relevant changes on symbol digit modalities test during the double-blind period.
- Whole brain atrophy measured by annualized rate of percent brain volume change.

Eligibility Criteria

Adult patients, aged 18 to 55 years (inclusive).
Patients with an established diagnosis of MS according to 2017 McDonald criteria[4].

Patients with relapsing MS comprising of relapsing-remitting MS and active secondary progressive MS, both defined according to the Lublin criteria 1996[5] and 2014[6].

Active disease defined by Lublin criteria 2014[6], evidenced prior to screening by:

- at least 2 relapses in last 24 months before randomization, or
- at least 1 relapse in last 12 months before randomization, or
- a positive Gd+ MRI scan (brain and/or spine) in the last 12 months prior to randomization.

ENSURE:
Positive Outcome of Interim Futility Analysis

- Unblinded Independent Data Monitoring Committee (IDMC) confirmed predetermined **futility criteria have not been met**
- IDMC recommended **continuing trial without changes,** including **no need for potential upsizing**
- Interim analysis was pre-planned after about half of expected first relapse events occurred in the double-blinded treatment periods
- Based on a conditional power analysis by an unblinded IDMC
- Immunic has remained blinded and has not seen any of the data available to the IDMC to make their recommendations

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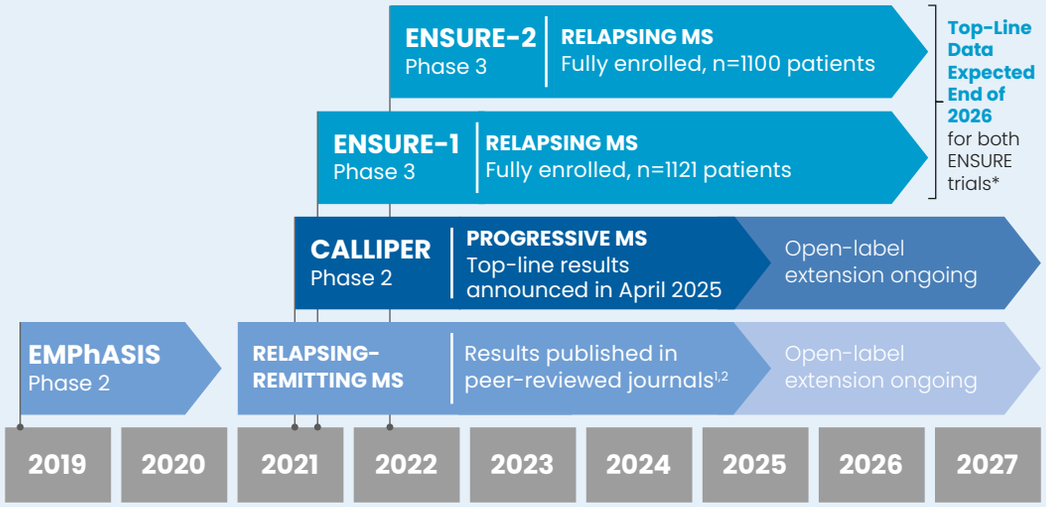
Clinical Trials Overview in Multiple Sclerosis (MS)



*Top-line data are currently anticipated by the end of 2026. Timelines are subject to change based on study progress.

Proposed Mode of Action Based on Preclinical Studies

Nurr1 activation – known neuroprotective target

Nurr1 activation by vidofludimus calcium improves the survival of neurons in a neurotoxic environment *in vitro*[7]. Vidofludimus calcium also reduces the activation of microglia and the production of neurotoxic and inflammatory mediators *in vitro*[7].

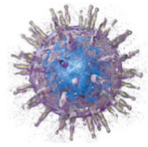
DHODH inhibition – immunomodulatory effects

Vidofludimus calcium selectively inhibits enzyme dihydroorotate dehydrogenase (DHODH). This leads to reduced proliferation of highly active immune cells involved in MS *in vitro, and reduced* focal inflammation and associated MRI activity as shown in the phase 2 trial in participants with RRMS[1,2,8].

Blocking of Th17/Th1 cytokines

DHODH inhibition – antiviral effects

DHODH inhibition depletes pyrimidine nucleotides that are needed for production of viral RNA and DNA as well as viral proteins (via mRNA). Through this host-based mechanism vidofludimus calcium shows broad antiviral effects, including anti-EBV activity *in vitro*[9,10].



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References

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Legal notice

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