THE DHODH INHIBITOR IMU-838/VIDOFLUDIMUS CALCIUM SHOWS A SUPERIOR COMPOUND PROFILE AS COMPARED TO THE APPROVED DHODH INHIBITOR, TERIFLUNOMIDE

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Background: The dihydroorotate dehydrogenase (DHODH) inhibitor teriflunomide, approved for the treatment of Relapsing-Remitting Multiple Sclerosis (RRMS), is known (according to information in the prescribing information)[1] to have significant adverse events, including diarrhea, alopecia, rash, and liver enzyme elevation. Immunic is developing a new chemical entity DHODH inhibitor, vidofludimus, with no structural similarity to teriflunomide.

Goal: The objective of the investigations was to explore the profile of IMU-838 (the calcium salt form of vidofludimus) and to contrast it to teriflunomide.

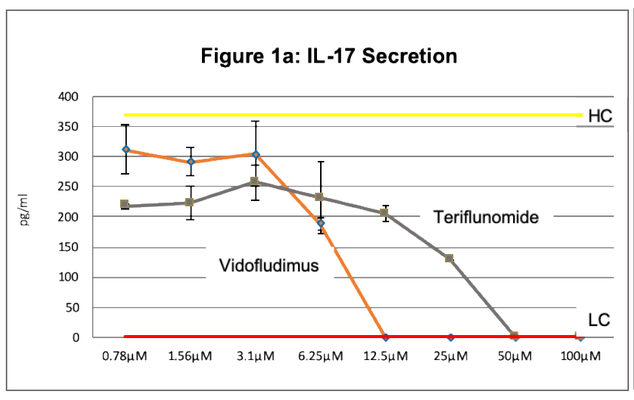
Conclusion: The novel DHODH inhibitor vidofludimus demonstrated a highly favorable profile regarding safety, biological selectivity, pharmacokinetics (PK) and potency. Many of the adverse effects that are known from the safety profiles of the FDA-approved DHODH inhibitor teriflunomide, including alopecia, diarrhea, neutropenia, were observed at a rate following vidofludimus treatment similar to placebo. This is believed to be due to the high selectivity of vidofludimus for DHODH and a distinct absence of off-target effects. These data along with its selective immunomodulatory activity make vidofludimus a promising therapeutic candidate for patients with RRMS.

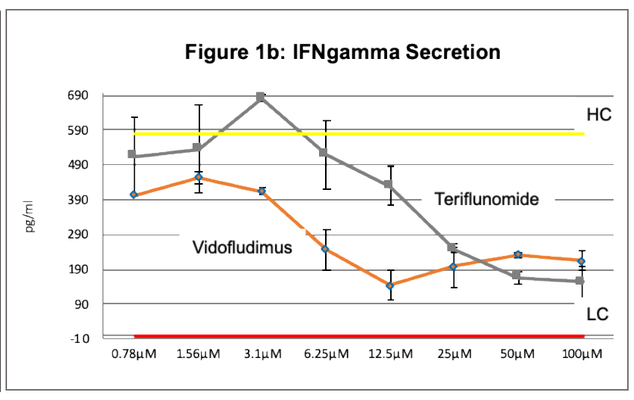
A Phase 2 clinical trial of IMU-838 in RRMS is currently ongoing and top-line data is expected to be available in Q3/2020.

Topic 1 – Highly potent cytokine inhibition

Human PBMCs were stimulated with PHA for 44 hours and treated with different concentrations of vidofludimus or teriflunomide. Cytokine secretion of IL-17 (Figure 1a) and IFNγ (Figure 1b) was measured by Luminex.

CONCLUSION:
In a study designed to determine the secretion levels of important cytokines, it was shown that IMU-838 exhibits a higher potency than teriflunomide on cytokine reduction in stimulated human PBMCs.





Topic 2 – Ideal pharmacokinetic profile for once daily dosing

In a double blind, placebo controlled, parallel group design Phase 1 study with escalating multiple doses of IMU-838 (vidofludimus calcium), subjects were randomized to receive placebo or IMU-838 (14-day once daily administration). Blood samples for were collected for IMU-838 concentrations and analyzed using a validated LC-MS/MS method.

In this human PK study, the plasma half-life of IMU-838 was determined to be about 30 hours with no loading dose required. Peak concentration in blood plasma was reached at about 3 hours after taking the IMU-838 tablets.

Dose of IMU-838 [mg]	30	40	50
Median tmax (h)	3	3	3
t1/2 (h)	30.4	28.6	29.7
C-through (µg/mL) at Day 8	3.2	4.6	4.9

Steady state concentration (C-trough) was reached after 5 to 7 days (Figure 2). At 10 days after the last dose administered, no detectable blood level of IMU-838 was found in any of the study subjects with doses of 30 mg once daily (and in 7/8 subjects of 40 mg and in 12/16 subjects of 50 mg).

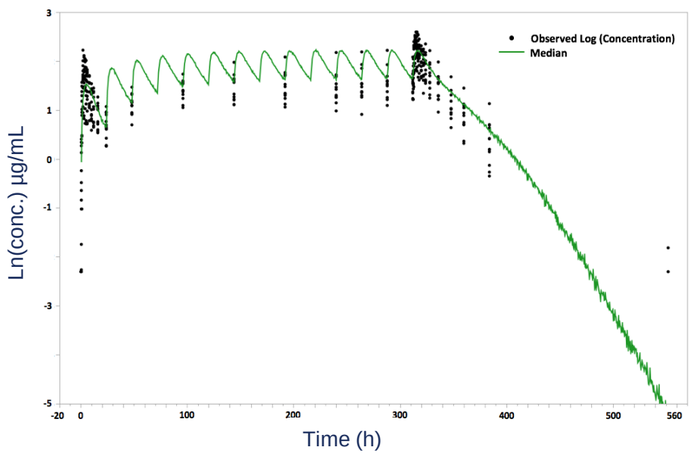
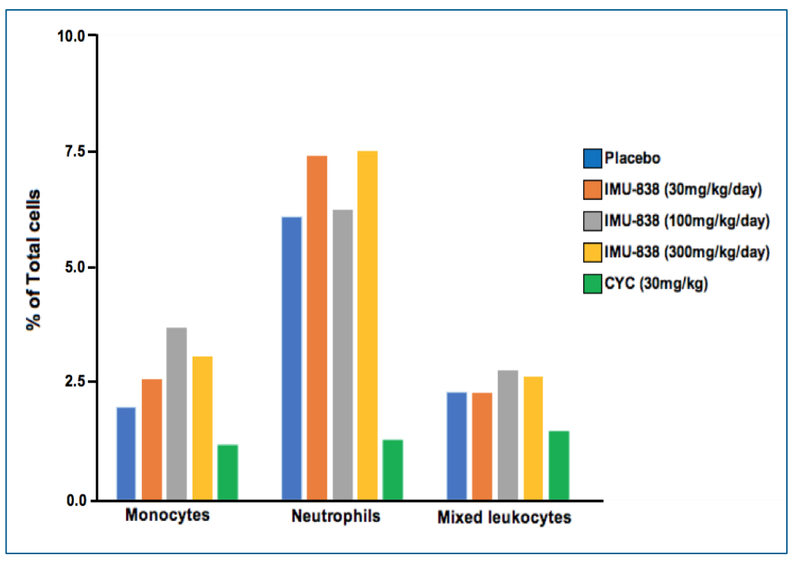


Figure 2: Observed pharmacokinetic data from 40 mg once daily IMU-838 (14-day Multiple Ascending Dose Phase 1 study) and derived population PK Model

CONCLUSION:
The pharmacokinetic properties of IMU-838 are well suited for once daily dosing, as well as for the rapid discontinuation of the drug, if needed.

Topic 3 – Biological selectivity without general antiproliferative effects



The biological selectivity of vidofludimus was tested in a mouse model. The animals received a 100µl suspension of IMU-838 containing 30, 100 or 300 mg/kg/day, respectively for 10 weeks. A placebo group was also included. A control group received a weekly dose of 30mg/kg cyclophosphamide (CYC) which is known to strongly suppress the bone marrow activity. The results showed that IMU-838 has no effect on the number of bone marrow cells, even at the highest dose. The results from this study are shown in Figure 3.

Figure 3. Vidofludimus and bone marrow cells in $MRL^{lpr/lpr}$ mice. Flow cytometry was used to quantify neutrophils and monocytes in bone marrow of 22-week-old female mice from all treatment groups. Monocytes were identified as $7/4^{bri}$ $Ly6G^{-}$. Neutrophils were identified as $7/4^{+}Ly6G^{+}$.

Data is shown as mean percentages from at least five to six mice in each group.

Graph is adapted from publication Kulkarni et al.

CONCLUSION:
This investigation shows that the DHODH inhibitor vidofludimus has no general antiproliferative effect on immune cells (as exemplified on bone marrow) while its mechanism of action works via immune-metabolic effects on activated lymphocytes with a high metabolic turnover only.

Topic 4 – No increased rate of Diarrhea, Alopecia, and Neutropenia

Some of the most common adverse reactions of the current FDA-approved DHODH inhibitor teriflunomide include diarrhea, alopecia, and neutropenia[1], which may have contributed to the high rates of treatment discontinuation.[6]

The COMPONENT study was a randomized, double blind, placebo-controlled, parallel group, multicenter Phase 2 clinical trial to assess the safety and efficacy of vidofludimus in combination with methotrexate (MTX) in patients with rheumatoid arthritis (RA) who were not responding sufficiently to MTX monotherapy. Patients with active RA were enrolled and randomized into two treatment arms, receiving either once-daily vidofludimus or placebo in combination with the patient's current established stable once-weekly dose MTX. The safety set includes all patients who were randomized and received any amount of study drug.

MedDRA SOC	MedDRA Preferred Term	Vido-fludimus (N = 122)	Placebo (N = 119)	Total (N = 241)
Gastrointestinal Disorders	Diarrhea	7 (5.7%)	7 (5.9%)	14 (5.8%)
Skin and Subcutaneous Disorders	Alopecia	1 (0.8%)	0 (0.0%)	1 (0.4%)
Blood and Lymphatic Disorders	White Blood Cell Disorders	0 (0.0%)	1 (0.8%)	1 (0.4%)
Investigations	Neutrophil Count Abnormal	0 (0.0%)	1 (0.8%)	1 (0.4%)

CONCLUSION:
The DHODH inhibitor vidofludimus has the same mechanism of action as the FDA approved teriflunomide. However, studies have shown that they differ in their safety profiles. While teriflunomide has a number of characteristic adverse effects (hypothesized to be caused by off-target effects on kinases)[3-5], the structurally unrelated vidofludimus lacks these specific side effects (as vidofludimus was not found to have off-target effects on more than 100 protein kinases examined, data on file by Immunic AG, but not shown here).

REFERENCES:

1) Prescribing information Aubagio®, available at: http://products.sanofi.us/Aubagio/aubagio.html

2) O. P. Kulkarni, S. G. Sayyed, C. Kanter, et al. 4SC-101, A Novel Small Molecule Dihydroorotate Dehydrogenase Inhibitor Suppresses Systemic Lupus Erythematosus in MRL-(Fas)lpr Mice. The American Journal of Pathology, 2010:176(6):2840-7.

3) Mattar T, Kochhar K, Bartlett R, Bremer EG, Finnegan A. Inhibition of the epidermal growth factor receptor tyrosine kinase activity by leflunomide. FEBS Lett. 1993;334(2):161-4.

4) Nikcevich DA, Finnegan A, Chong ASF, Williams JW, Bremer EG. Inhibition of Interleukin 2 (IL-2)-stimulated tyrosine kinase activity by leflunomide. Agents Actions. 1994;41(2):C279-C82.

5) Xu X, Williams JW, Bremer EG, Finnegan A, Chong AS-F. Inhibition of Protein Tyrosine Phosphorylation in T Cells by a Novel Immunosuppressive Agent, Leflunomide. J Biol Chem. 1995;270(21):12398-403

6) Johnson KM, Zhou H, Lin F, Ko JJ, Herrera V. Real-World Adherence and Persistence to Oral Disease-Modifying Therapies in Multiple Sclerosis Patients Over 1 Year. J Manag Care Spec Pharm. 2017 Aug;23(8):844-852.