IMU-838: A Safe and Potent Inhibitor Of DHODH for the Treatment of Autoimmune Disease: Mechanism of Action and Clinical Outcomes

NASDAQ: IMUX | October 06, 2021
B &T Cell-Mediated Autoimmune Disease Drug Development Summit
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Forward-looking statements included in this presentation are based on information available to Immunic as of the date of this presentation. Immunic does not undertake any obligation to update such forward-looking statements except as required by applicable law.
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Immunic Therapeutics

Company Introduction
Our Mission

We are developing a pipeline of next-generation selective oral therapies focused on offering patients with chronic inflammatory and autoimmune diseases new and clinically meaningful treatment options.
# Development Pipeline

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<th>Program</th>
<th>Target</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Key 2021/22 Milestones</th>
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<tbody>
<tr>
<td>IMU-838</td>
<td>DHODH</td>
<td>Relapsing-Remitting Multiple Sclerosis (RRMS)</td>
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<td>• Phase 3 RRMS: first-patient-in expected in Q4/2021</td>
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<td>Progressive Multiple Sclerosis (PMS)</td>
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<td>• Phase 2 UC: last-patient-in expected in Q4/2021; top-line data expected in Q2/2022</td>
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<td>Ulcerative Colitis (UC)</td>
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<td>Crohn’s Disease (CD)</td>
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<td>Primary Sclerosing Cholangitis (PSC)</td>
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<td>IMU-935</td>
<td>RORyt</td>
<td>Psoriasis</td>
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<td>• Phase 1 healthy volunteers: unblinded SAD/MAD safety data expected in Q4/2021</td>
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<td>Castration-Resistant Prostate Cancer (CRPC)</td>
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<td>• Phase 1b psoriasis: initial psoriasis data expected in Q2/2022</td>
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<td>Guillain-Barré Syndrome (GBS)</td>
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<td>• Phase 1 CRPC: expected to start in Q4/2021</td>
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<td>IMU-856</td>
<td>Intestinal Barrier Function</td>
<td>Gastrointestinal Diseases</td>
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<td>• Phase 1 healthy volunteers: unblinded SAD/MAD safety data expected in Q1/2022</td>
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- Completed or ongoing
- In preparation or planned
IMU-838 Overview

Mode of Action

Clinical Data
Blocking DHODH Leads to a Selective Effect on Overactivated Lymphocytes Without Broader Immunosuppression

Selective targeting of hyperactivate immune cells without affecting normal immune function

No negative effect observed on:
- White blood cell count
- Rates of infection or malignancy
- Vaccination efficacy\(^1\)

**Lymphocyte**
- Metabolically silent
- DHODH not important

**Activated Lymphocyte**
- Activation of pyrimidine de novo synthesis
- DHODH upregulation
- Rate limiting step in pyrimidine synthesis

**“Stressed” Lymphocyte**
- IMU-838 triggering:
  - Pyrimidine pool depletion
  - Metabolic stress signal up

**Pharmacological Effects**
- Blocking of Th17/Th1 cytokines

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DHODH: dihydroorotate dehydrogenase
Highly Potent Cytokine Inhibition

- Human PBMCs were stimulated with PHA for 48h and treated with different concentrations of vidofludimus* (Vido) or teriflunomide (TNFM)
- Cytokine secretion of IL-17 and IFNγ was measured by ELISA

**Muehler et al., 2020**
* vidofludimus is the active moiety of IMU-838

**IMU-838 Exhibits A High Potency On Cytokine Reduction**
Hyperactive/high-affinity immune cells are specifically dependent on DHODH

High metabolic turnover in high-affinity T cells

High amounts of nucleotides for mRNA synthesis (up to 100-fold higher nucleotide demand for RNA synthesis than for DNA synthesis)

High producers of IL-17 and IFNγ
IMU-838 Is Highly Active on Murine High Affinity T Cells

IMU-838 selectively blocks proliferation of T cells in antigen dependent manner

CD8+ T cells from OT-I (high affinity TCR) and OT-III (low affinity TCR) mice were stimulated with OVA peptide loaded splenocytes (antigen specific) in the presence or absence of 10 µM IMU-838 and Teriflunomide (TF) for 3 days.

Read out: proliferation

→ Strong inhibition of high affinity T cells but not low affinity T cells

Murine DHODH Inhibition IC_{50}: 5 µM IMU-838, 0.2 µM Teriflunomide

Ref: Collaboration Luisa Klotz, Muenster, Germany
IMU-838 Promotes a Less Inflammatory Environment

Stopping a pro-inflammatory environment

→ Repression of pro-inflammatory cytokines

IL-17A/F, IFNγ, IP-10

GM-CSF, IL-6, IL-1β

→ Anti-inflammatory cytokine induction

IL-4, IL-10

Induction of apoptosis in stimulated PBMCs

10 µM IMU-838 (Vido) induces similar % of apoptosis compared to 100 µM teriflunomide (TNFM)

Induction of regulatory macrophages in MLR

Moderate induction of regulatory macrophages and strong additive effect in combo with Infliximab

1 Peripheral Blood Mononuclear Cells, 2 Mixed Lymphocyte Reaction, 3 6-thioguanin
Kohlhof et al., Poster UEGW 2019; Muehler et al., 2020
No General Antiproliferative Effects by IMU-838

IMU-838 did not induce monocyto-, neutro- and leukopenia in a mouse model of SLE

- Indicating a significantly lower bone marrow toxicity compared to Cyclophosphamide

IMU-838 has a natural selectivity towards hyperactivate immune cells and exhibits no general immune suppressive features

SLE: Systemic Lupus Erythematosis

Graph is adapted from Kulkarni et al., Am J Pathol. 2010 Jun;176(6):2840-7. Epub 2010 Apr 22
Muehler et al., ECTRIMS 2019, Abstract A-1026-0031-00242
IMU-838 Demonstrated Activity in a Therapeutic RRMS Animal Model

IMU-838 demonstrates dose-dependent activity in rat EAE model

- Improvement of body weight for all doses tested
- Improvement of disease severity for 20 and 60 mg/kg

Muehler et al., 2020
RRMS: Relapsing-Remitting Multiple Sclerosis
IMU-838 (Vidofludimus Calcium): Key Characteristics

Oral small molecule

- Active moiety vidofludimus MW 355 g/mol
- IMU-838 is calcium salt of vidofludimus

Chemical name (IUPAC):
2-(3-Fluro-3’-methoxybiphenyl-4-ylcarbamoyl)-cyclopent-1-enecarboxylic acid

Small white tablet

- Oral
- Once or twice daily
- Human serum t_{1/2} ~ 30 hours
- Human t-max ~ 2-3 hours
14 Day Multiple Dosing of 35 mg Vidofludimus in Humans – Corresponds to 30 mg IMU-838

Estimated Average Exposure at steady state

- IC\textsubscript{90} IL-17F and IFN\textsubscript{\gamma} in PBMCs
- IC\textsubscript{50} apoptosis of act. T-cells
- IC\textsubscript{50} IFN\textsubscript{\gamma} (~ 1.3 µg/ml) in PBMCs
- IC\textsubscript{50} hDHODH (= 0.088 µg/ml)

At 35 mg vidofludimus (~30 mg IMU-838), exposure in patients is continuously above the 90 % inhibition level (IC\textsubscript{90}) of IL-17F and IFN\textsubscript{\gamma}.
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IMU-838 | Clinical Data

- Inflammatory Bowel Disease (IBD)
- Multiple Sclerosis (MS)
ENTRANCE Study: Primary Efficacy Results

Study performed with active moiety vidofludimus

All patients failed two attempts to taper down steroids

Open-label, dosing of 35 mg vidofludimus QD

Primary efficacy endpoint: steroid-free/steroid-reduced remission (week 12)

Number of Patients

Week 1: 26.5 (± 8.0) mg*

Week 12: 1.0 (± 2.8) mg*

IMU-838 had response rates of:

85.7% in Crohn’s disease

91.7% in ulcerative colitis

Herrlinger et al., 2011, Gastroenterology 140:588

*Mean dose of steroid equivalent in mg per day; mITT: modified intent to treat; QD: quaque die = once-daily
CALDOSE-1: Clinical Phase 2 in UC Ongoing
NCT03341962

Coordinating Investigator:
Dr. Geert d’Haens
(AMC Amsterdam)

Active IND in the United States

Primary Endpoint:
Proportion of patients with symptomatic remission and endoscopic healing at week 10

Overall Number of Patients: 240

Currently More Than 100 Active Sites in 14 Countries: USA, Western, Central and Eastern Europe

Timelines:
Recruitment expected to be completed in Q4/2021
Currently estimated to deliver top-line data in Q2/2022
CALDOSE-1: Phase 2 Trial Design in UC
NCT03341962

**Induction Phase**
- Placebo (n=60)
- 10 mg IMU-838 QD (n=60)
- 30 mg IMU-838 QD (n=60)
- 45 mg IMU-838 QD (n=60)

10 weeks

**Maintenance Phase**
- Patients with symptomatic remission at weeks 10 or 22
  - Placebo (n=60)
  - 10 mg IMU-838 QD
  - 30 mg IMU-838 QD

Final analysis induction phase after 10 weeks

Final analysis maintenance phase after 50 weeks

Optional open-label extension period to obtain long-term safety: up to 9 years

R: randomization; QD: quaque die = once-daily

Patient number required: N=240

Until UC relapse or termination
The interim analysis supported that IMU-838 is a safe oral medication in patients with UC with a broad therapeutic index.

• Performed by an unblinded data review committee (DRC) in August 2019
• Analysis based on all available clinical, endoscopic, biomarker, pharmacodynamic, and safety data

1 Main Treatment Period
• Doses of 10 to 45 mg may be effective in UC

2 Interim Analysis Confirmed the Good Safety Profile
• No intolerable dose identified
• No safety signal observed
IMU-838 | Clinical Data

- Inflammatory Bowel Disease (IBD)
- Multiple Sclerosis (MS)
Phase 2 Data of IMU-838 in RRMS: Primary and Key Secondary Endpoints Met, Showing Strong Activity

Coordinating Investigator
Robert Fox, MD (Cleveland Clinic)

Double-Blind, Placebo-Controlled, Randomized, Parallel-Group Phase 2 Trial
- Blinded main treatment period of 24 weeks
- Extended treatment period of up to 9.5 years to observe long-term safety
- 210 patients randomized in 36 centers across four European countries

Key Study Endpoints
Cumulative number of new combined unique active (CUA) magnetic resonance imaging (MRI) lesions up to week 24
- Primary endpoint: Difference between 45 mg IMU-838 & placebo
- Key secondary endpoint: Difference between 30 mg IMU-838 & placebo

Suppression of CUA MRI Lesions IMU-838 Versus Placebo Over 24 Weeks

CUA MRI Lesions: combined unique active magnetic resonance imaging lesions. Sum of the number of all new Gadolinium-enhancing lesions on T1-weighted MRI and the number of all new or substantially enlarged lesions on T2-weighted MRI (non-enhancing on T1-weighted MRI), avoiding double counting. Estimates are adjusted for baseline volume of T2 lesions, MRI field strength (1.5 or 3.0 Tesla), and baseline number of Gadolinium-enhancing 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.
Study Met Key Secondary Endpoints: Suppression of MRI Lesions and Robust Decrease in Serum Neurofilament Light Chain

- Effect of IMU-838 on MRI lesion suppression can be observed already at early time points
- Robust decrease in serum neurofilament light chain

Cumulative Number of Gd+ Lesions*

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<thead>
<tr>
<th></th>
<th>BL</th>
<th>W6</th>
<th>W12</th>
<th>W18</th>
<th>W24</th>
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<td>4</td>
<td>6</td>
<td>8</td>
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<tr>
<td>45 mg IMU-838</td>
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<td>4</td>
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<tr>
<td>Placebo</td>
<td>0</td>
<td>2</td>
<td>6</td>
<td>10</td>
<td>18</td>
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Median Percentage Change from Baseline to Week 24 in Serum Neurofilament (Including 95% Confidence Intervals) (Biomarker for Axonal Damage)**

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<tbody>
<tr>
<td>30 mg IMU-838</td>
<td>-17.0%</td>
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</tr>
<tr>
<td>45 mg IMU-838</td>
<td>-20.5%</td>
<td>+6.5%</td>
</tr>
<tr>
<td>Placebo</td>
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* 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)

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

Gd: Gadolinium
Phase 2 Data of IMU-838 in RRMS: Positive Signals on Relapse and Unconfirmed Disability

Left: Proportion of Patients With Relapse up to Week 24. Right: EDSS (Expanded Disability Status Scale) progression is defined as an increase of the EDSS score compared to baseline of at least 1.0 point for patients with a baseline EDSS score of 1 to 4.0 or of at least 1.5 points for patients with a baseline EDSS score of 0. There is no confirmation of EDSS progression in this trial due to its short duration. Patients with missing assessments at week 24 without a progression at any time are set to missing.
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IMU-838

Broad-Spectrum Antiviral Activity

Mode of Action and Antiviral Effect
Summary of Rationale for IMU-838 as an Antiviral Agent

- **Dual mode of action:** orally available DHODH inhibitor with both, antiviral and anti-inflammatory effects
- **Host-based mechanism:** avoids dependence on specific viral proteins and, therefore, offers broad-spectrum antiviral activity

**Uninfected Normal Cell**
- Metabolically silent
- DHODH not important

**Virus Infected Cell**
- Virus infection
- Viral replication starts
- Pyrimidine de novo synthesis activated
- DHODH inhibition

**Block of Pyrimidine de novo Synthesis**
- IMU-838
- DHODH block
- Pyrimidine pool
- Metabolic stress

**Antiviral Effects**
- Lack of nucleotides blocks:
  - viral mRNA synthesis
  - viral genomes
- Innate Immunity independent of Interferon

**Inhibition of virus replication**
- Plus attack by innate immunity
IMU-838 has shown broad-spectrum antiviral activity against different pathogenic viruses with EC$_{50}$ values well reachable with 22.5 mg BID dosing.

Antiviral vs. Immunomodulatory Treatments

Viral Replication

Direct Antiviral Therapies
Example: Remdesivir

Immune Overstimulation

Immunomodulators
Example: Tocilizumab

DHODH Inhibitors

Known Broad Antiviral Effects

Selective Immunomodulation

“Nucleotide starving”

Virus-infected host cells

Highly stimulated immune cells
Conclusions
Conclusions

- IMU-838 is a safe and orally available small molecule inhibitor of DHODH for the treatment of various autoimmune diseases.

- DHODH inhibition targets highly metabolically activate cells.

- Targeting DHODH has an additional broad-spectrum antiviral activity.