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Phase 1 Single Ascending Dose (SAD) Trial of ATI-2138, an Investigational Oral Covalent ITK/TXK/JAK3 (ITJ) Inhibitor

Preliminary Data

November 8, 2022

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ATI-2138: Covalent ITK/TXK/JAK3 (ITJ) Inhibitor with Potential for Ulcerative Colitis and other T Cell-Mediated Diseases

Background

- ATI-2138 covalently blocks ITK/TXK/JAK3[1]
  - Potential for synergistic efficacy
    - ITK/TXK required for T cell receptor (TCR) signaling
    - JAK3 required for γc cytokines (IL-2/4/7/9/15/21)
  - PD effects persist after plasma clearance
- ATI-2138 is selective for T cell signaling[2,3]
  - Drugs like cyclosporine (CsA) inhibit calcineurin which is widely expressed
  - ATI-2138 targets unique kinases expressed only in immune cells
- ATI-2138 has the potential to treat T cell-mediated autoimmune diseases[4,5]

Status

- Phase 1 Single Ascending Dose Study successfully completed
- New IND submitted to Division of Gastroenterology in October 2022
- Pending FDA feedback, on track for start of Phase 1 Multiple Ascending Dose Study by end of 2022
- Phase 2a Proof of Concept study in Ulcerative Colitis under development

1. Data on file.
2. Graham RM. *Cleve Clin J Med.* 1994;61(4):308-313.
3. Siliciano JD, et al. *Proc Natl Acad Sci U S A*. 1992;89(23):11194–11198.
4. Robinson MF, et al. [published online ahead of print, 2020 May 18]. *Arthritis Rheumatol*. 2020.
5. Russell SM, et al. *Science*. 1995;270(5237):797-800.

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Study Design

N=64
8 Cohorts
6 Active/2 Control per arm

Cohort	No. Subjects	Planned Dose
1	8	1 mg
2	8	3 mg
3	8	5 mg
4	8	15 mg [1]
5	8	25 mg [2]
6	8	50 mg
7	8	50 mg [3]
8	8	80 mg

1. *Cohort 4 (food effect; fasted versus fed)*
2. *Cohort 5 (formulation bridging; tablet versus capsule)*
3. *Cohort 7 (50 mg cohort repeated due to higher than expected variability in cohort 6)*

Eligibility

- Healthy subjects age ranging from 18 to 55 years, inclusive at screening
- Minimum weight of 50 kg
- Body mass index of 18 to 32 kg/m^2, inclusive

Objectives

Primary
- To assess safety, tolerability and pharmacokinetics (PK) profile of ATI-2138 following single oral doses of ATI-2138 in healthy subjects

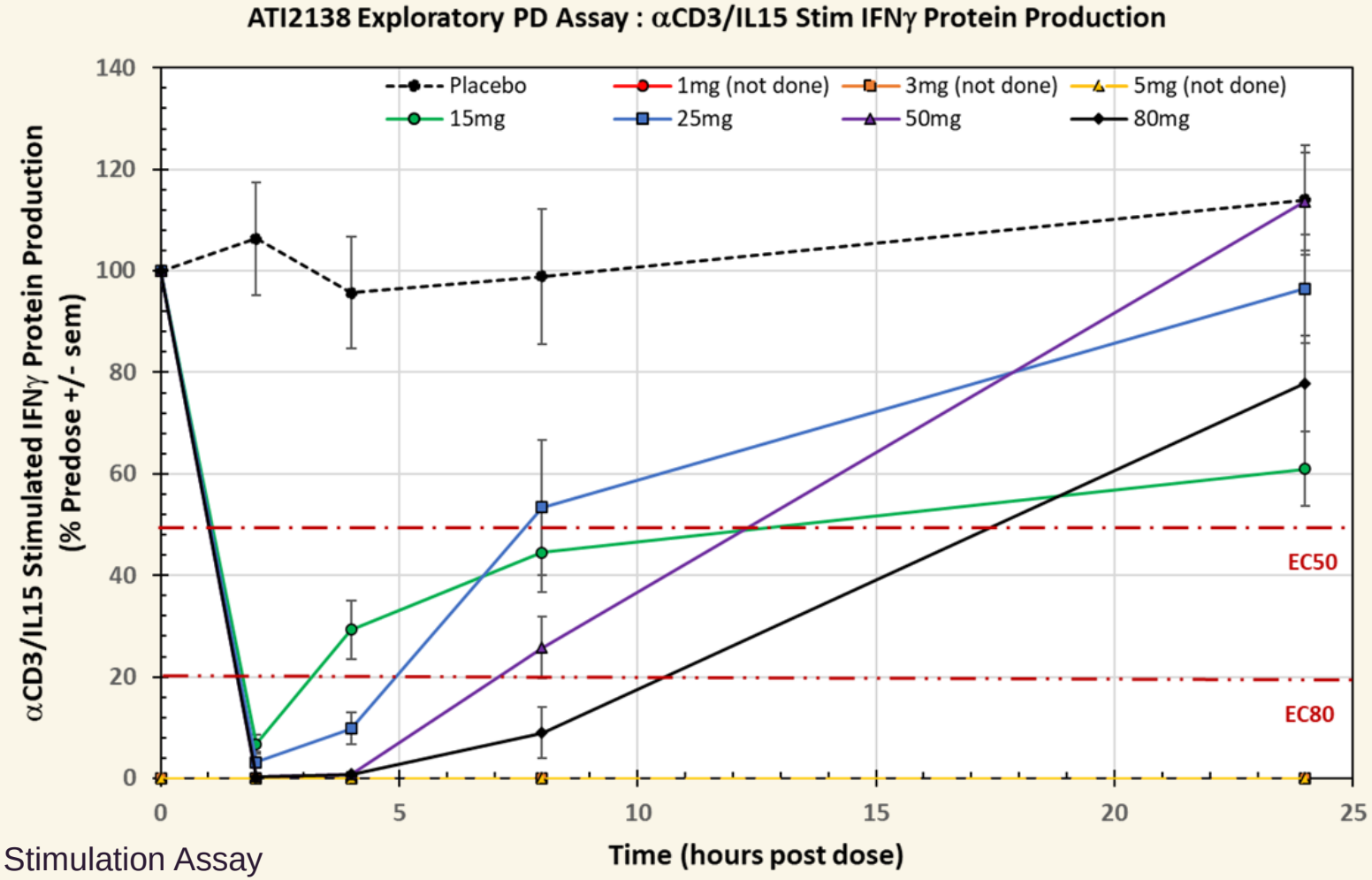
Secondary
- To assess the effect of food on the PK of ATI-2138 following administration of a single oral dose of ATI-2138
- To assess the effect of formulation (tablet versus capsule) on the PK of ATI-2138 following administration of a single oral dose of ATI-2138
- To explore the pharmacodynamic (PD) response to ATI-2138 following single oral dose of ATI-2138

Preliminary Data

- Safety
  - ATI-2138 was generally well tolerated at all doses tested in the trial. No serious adverse events or severe adverse events were reported. The most common adverse events in subjects treated with ATI-2138, headache (four subjects) and lightheadedness (two subjects), were mild and transient.
- PK
  - The PK data were linear, and absorption was linear. This shows that ATI-2138 has a favorable PK profile up to 80 mg single dose.
  - Terminal half-life ranged from 1.5 – 2.5 hours.
  - No significant food effect at 15 mg (fasted versus fed) was observed.
  - Similar PK was observed with the capsule versus tablet formulations at 25 mg.
- PD
  - Dose-dependent inhibition of both ITK and JAK3 exploratory PD biomarkers was observed.
    - Near complete inhibition of the dual ITK and JAK3-stimulated IFNγ protein production was observed at the 15 mg through 80 mg doses.

Simultaneous Stimulation of the ITK and JAK3 Pathways was Dose-Dependently Inhibited by ATI-2138

Assesses modulation of both ITK and JAK3 via αCD3/IL-15-induced IFNγ protein production



Pharmacodynamic Dual Stimulation Assay