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KINOME INNOVATION

ATI-2138: An Investigational Novel Covalent ITK-JAK3 Inhibitor for T-Cell Mediated Diseases

18 Sep 2023

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ATI-2138: Combined IL-2-Inducible Tyrosine Kinase (ITK) & JAK3 Inhibitor for Autoimmune Disease

- ATI-2138 is an oral compound which interrupts T cell receptor (TCR) signaling by inhibiting ITK and JAK3 signaling of common γ chain cytokines in lymphocytes (including IL-2 & IL-15)
- ATI-2138 potently and selectively inhibits ITK and JAK3 (with some activity at TXK)
- ATI-2138 has demonstrated the prevention of inflammation in animal models of colitis and arthritis
- Safety, pharmacology and toxicology studies have been completed and support further development
- Phase 1 SAD and MAD studies in healthy volunteers have been completed
  - ✓ ATI-2138 was generally well tolerated and no serious adverse events were reported
  - ✓ PK was dose proportional with adequate exposure to block ITK and JAK3 in PD biomarker assays
- Aclaris is evaluating ATI-2138 for the potential treatment of a number of T cell-mediated autoimmune diseases
- A Phase 2a ulcerative colitis trial is in protocol development and operational preparations are under way

The unique pharmacological profile of ATI-2138 provides opportunity for differentiation

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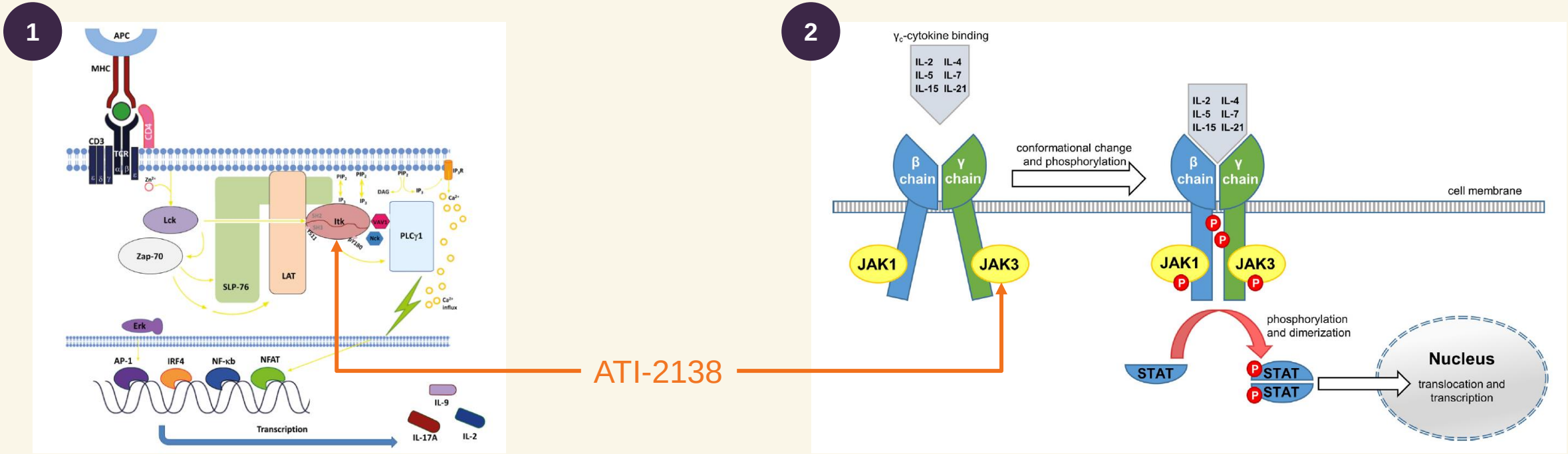
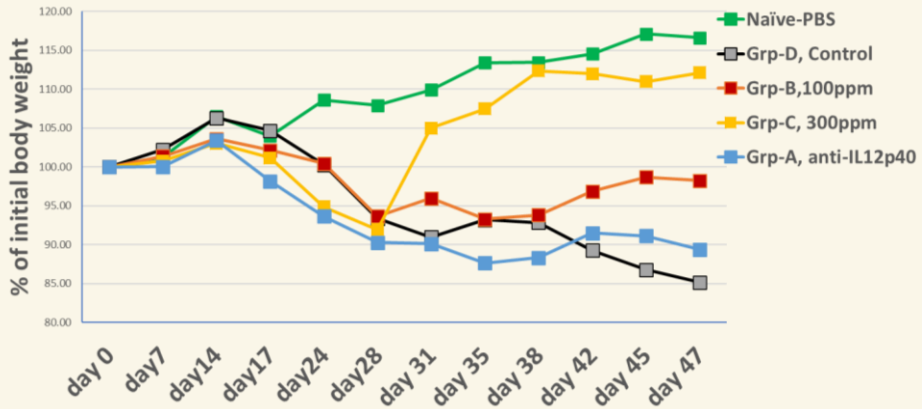
ATI-2138 is a Combined Covalent IL-2-Inducible Tyrosine Kinase (ITK) & JAK3 Inhibitor for Autoimmune Disease



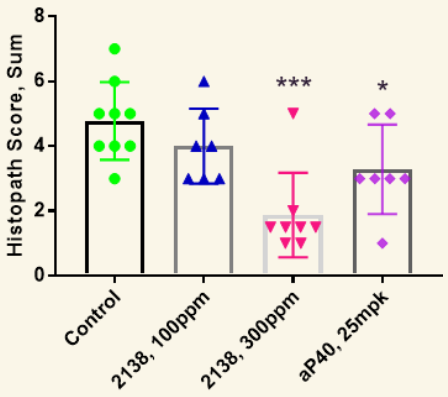
- ATI-2138 is an investigational oral compound which interrupts T cell receptor (TCR) signaling by inhibiting ITK and JAK3 signaling of common γ chain cytokines in lymphocytes (including IL-2 & IL-15) and is designed to reduce T cell differentiation, proliferation and cytokine production
- ATI-2138 is differentiated from other kinase inhibitors as it is highly potent for both ITK and JAK3 (IC50: 0.2nM ITK; 0.5nM JAK3)[3]
- Aclaris is evaluating ATI-2138 for the potential treatment of a number of T cell mediated autoimmune diseases including ulcerative colitis

1. Lechner KS, Neurath MF, Weigmann B. Role of the IL-2 inducible tyrosine kinase ITK and its inhibitors in disease pathogenesis. J Mol Med (Berl). 2020 98(10):1385-1395; 2. Forster M, Gehringer M, Laufer SA. Recent advances in JAK3 inhibition: Isoform selectivity by covalent cysteine targeting. Bioorg Med Chem Lett. 2017 15;27(18):4229-4237.; 3. Study Report SR03001

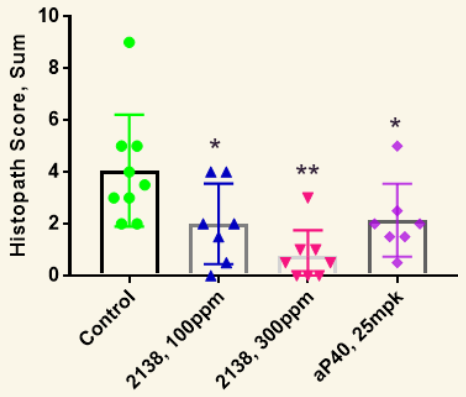
ATI-2138 Dose-Dependently Inhibited Inflammation in the Mouse T Cell Transfer Model of Inflammatory Bowel Disease



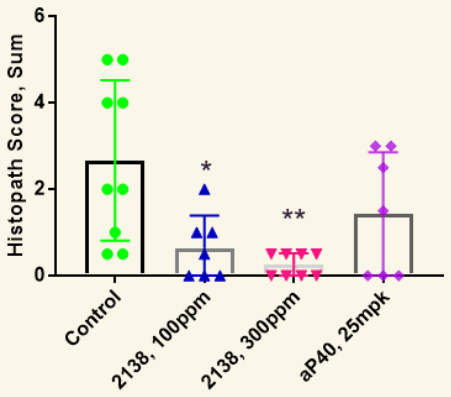
Proximal Colon



Distal Colon



Ileum



ATI-2138 inhibited colitis in the mouse T cell transfer model[1,2,3]

ATI-2138 dose-dependently decreased inflammation in proximal and distal colon, and ileum

Greater effect than anti-IL12 (P40) that significantly decreased inflammation in the proximal and distal colon

1. Study report SR03048; 2. CD4+CD45RB high naïve T cells injected to SCID mice; 3. *p<0.05, **p<0.01, ***p<0.001, vs Control group

ATI-2138 Phase 1 Multiple Ascending Dose Study Design

N=60

5 Cohorts

2 Weeks of Treatment

8 Active and 2 Placebo Subjects per Arm

Eligibility

- Healthy subjects age ranging between 18 and 55 years of age, inclusive at screening
- Minimum weight of 50 kg
- Body mass index of 18 to 32 kg/m2, inclusive

Cohort	No. Subjects	Dose
1	10	5 mg BID
2	10	15 mg BID
3a	10	30 mg QD[1]
3b	10	10 mg TID[1]
4	10	25 mg BID
5	10	40 mg BID

Objectives

- Primary
  - ✓ To assess the safety and tolerability of ATI-2138 following multiple oral doses of ATI-2138 in healthy participants
- Secondary
  - ✓ To explore the pharmacokinetic (PK) profile of ATI-2138 following multiple oral doses of ATI-2138 in healthy participants
- Exploratory
  - ✓ To explore the pharmacodynamic (PD) response to ATI-2138 following multiple oral doses of ATI-2138 in healthy participants

1. Not part of dose escalation

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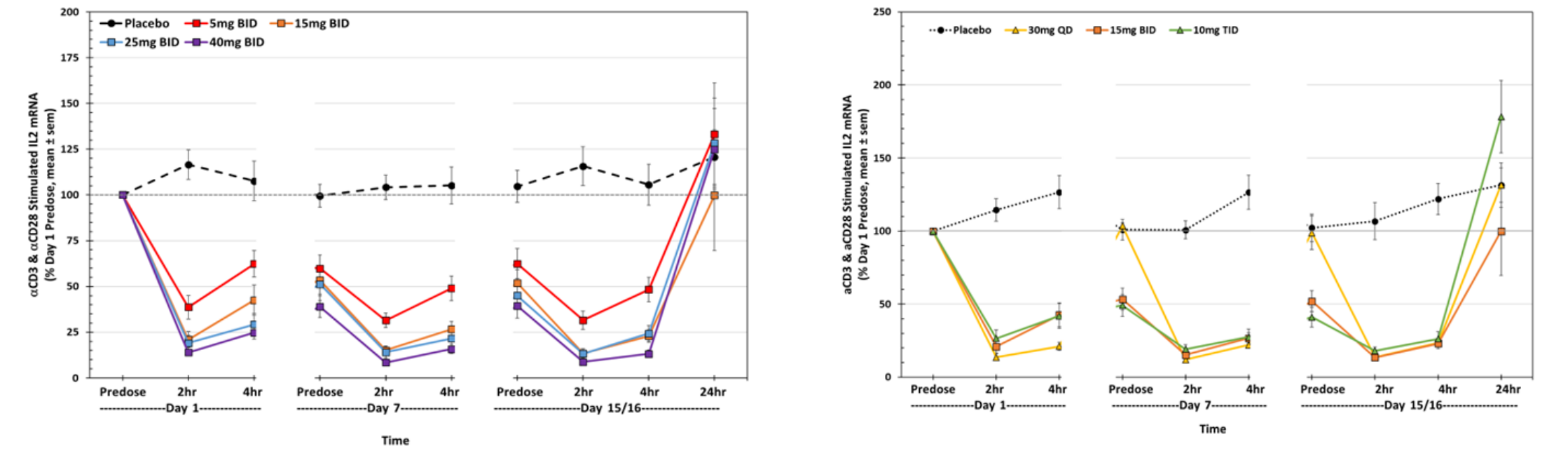
Dose-dependent Inhibition of Both ITK and JAK3 Exploratory PD Biomarkers was Observed in MAD Study

Anti-CD3 & anti-CD28 Stimulated IL-2 mRNA Expression (BID Cohorts left; 30mg Daily Cohorts right)



- Pharmacodynamic biomarkers - Ex-vivo stimulation of whole blood taken from subjects before and after administration of ATI-2138
- Stimulation with anti-CD3 and anti-CD28 (readout IL-2 mRNA; T-cell activation) – shown above, IL-15 (readout IFNγ; JAK1/3 activation) – not shown, and dual stimulation (readout IFNγ; T-cell and cytokine stimulation) – not shown
- ATI-2138 showed dose and time dependent inhibition of all stimulation conditions
- ATI-2138 30-80mg daily doses inhibited biomarker readouts by ~50-90% across the dosing intervals

Source – Data on file

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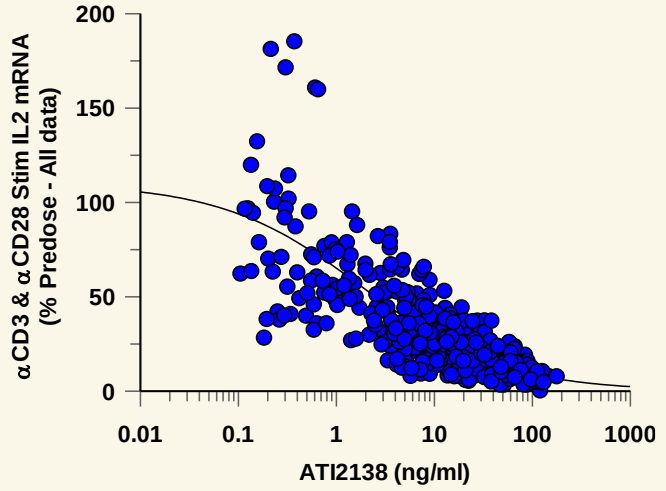
High Potency of ATI-2138 for ITK and JAK3 Observed in Preclinical Studies is Maintained in the SAD/MAD Clinical Study

αCD3 & αCD28 stim IL-2 mRNA

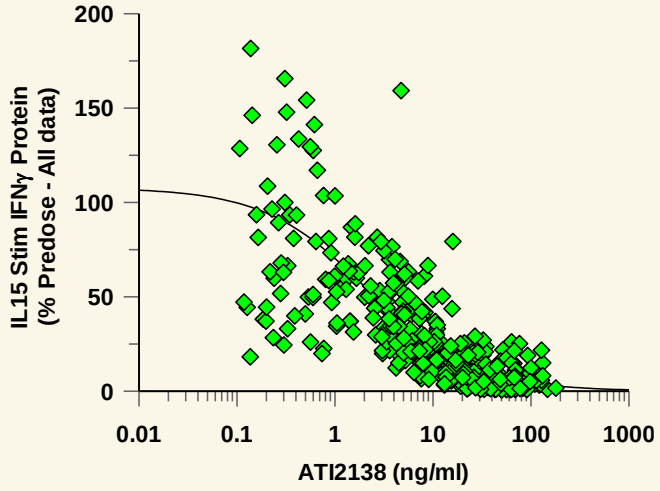


MAD EC_{50} : 1.9ng/ml / 5.3nM

SAD EC_{50} : 5.5ng/ml / 15.2nM

Preclinical IC_{50}* : 7.7ng/ml / 21.3nM

IL15 stim IFNγ protein

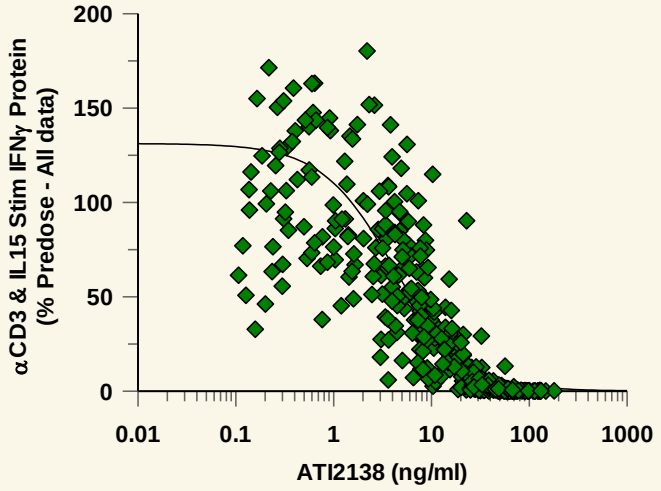


2.2ng/ml / 6.1nM

(not done)

2.9ng/ml / 8.0nM

αCD3 & IL15 stim IFNγ protein



4.1ng/ml / 11.4nM

2.6ng/ml / 7.3nM

3.6ng/ml / 10.1nM

- Exposure response data in Phase 1 SAD and MAD clinical studies
- ATI-2138 potency comparison to preclinical cell assay data
- No significant change when comparing Day 1, 7 & 15 EC_{50} values

1. Assay configured slightly different from clinical assay

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ATI-2138 Multiple Ascending Dose: Preliminary Data Summary

Safety

- ATI-2138 was generally well tolerated at all doses tested in the trial.
- No serious adverse events were reported.
- The most common adverse events in subjects treated with ATI-2138, and the only events occurring in more than 1 subject, were headache (2 subjects on 5 mg BID, 1 on 40 mg BID, all mild, resolved) and diarrhea (2 subjects on 5 mg BID– both single episodes, both mild).

Pharmacokinetics

- ATI-2138 was rapidly absorbed and cleared from the human body.
- Multiple doses ranging from 10 to 80 mg daily over two weeks in healthy volunteers showed linear PK and dose-dependent increases in exposure.
- At 30 mg daily, ATI-2138 plasma concentration reached the targeted level established using preclinical data.

Pharmacodynamics

- 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 15 mg BID, with minimal incremental benefit at higher doses.

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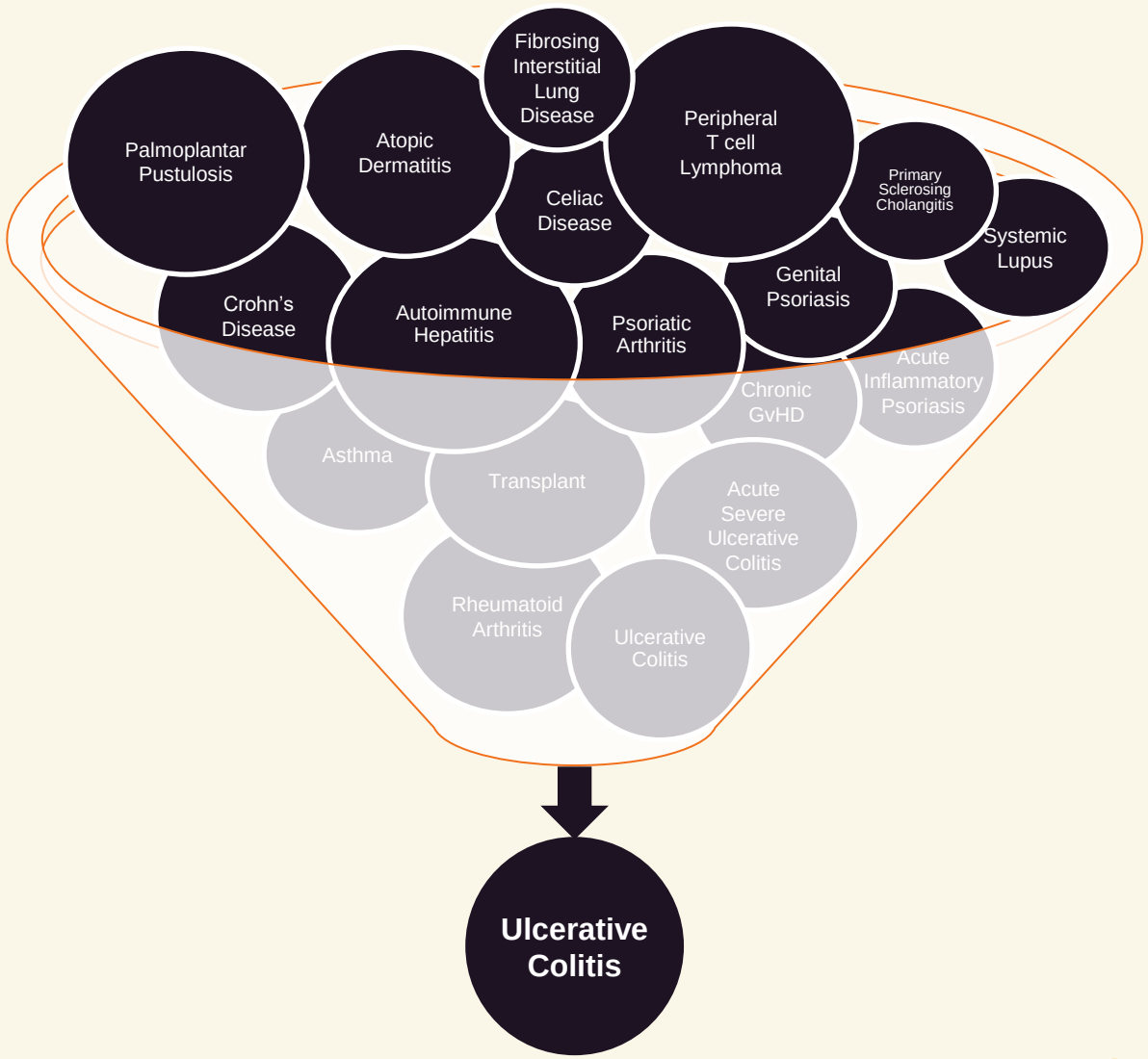
Initial Proof of Concept Trial in Ulcerative Colitis is Planned

- Cyclosporin A (CsA) is approved to treat UC and the mechanism of action is potentially related to inhibition of ITK in mucosal CD4+ T cells in animal models[1]
- The capacity of CsA to reduce experimental colitis may be dependent on ITK[1]
- Genetic inactivation of ITK prevented experimental colitis in 3 separate IBD models[1]
- ATI-2138 treatment suppressed established colitis in the mTCT model[2]



1. Lechner K et al. 2021. Gastroenterology;161(4):1270-1287.e19; 2. Study Report SR03048