EMPOWERING PATIENTS THROUGH KINOME INNOVATION

41st Annual J.P. Morgan Healthcare Conference

January 2023

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Cautionary Note Regarding Forward-Looking Statements

Any statements contained in this presentation that do not describe historical facts may constitute forward-looking statements as that term is defined in the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as “believe,” “expect,” “may,” “plan,” “potential,” “will,” and similar expressions, and are based on Aclaris' current beliefs and expectations. These forward-looking statements include expectations regarding Aclaris’ development of its drug candidates, including the timing of its clinical trials and regulatory submissions, and its expected cash runway. These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements. Risks and uncertainties that may cause actual results to differ materially include uncertainties inherent in the conduct of clinical trials, Aclaris' reliance on third parties over which it may not always have full control, the uncertainty regarding the COVID-19 pandemic including its impact on the timing of Aclaris’ regulatory and research and development activities, and other risks and uncertainties that are described in the Risk Factors section of Aclaris’ Annual Report on Form 10-K for the year ended December 31, 2021 and other filings Aclaris makes with the U.S. Securities and Exchange Commission from time to time. These documents are available under the “SEC Filings" page of the “Investors” section of Aclaris' website at http://www.aclaristx.com. Any forward-looking statements speak only as of the date of this presentation and are based on information available to Aclaris as of the date of this presentation, and Aclaris assumes no obligation to, and does not intend to, update any forward-looking statements, whether as a result of new information, future events or otherwise

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. These data involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk

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Biotechnology Company Focused on the Kinome
People + Platform + Pipeline

Leadership

Scientific Discovery led by World Class Kinase Expertise

- Kinome experts skilled at developing novel kinase targeted medicines

Proven Operational and Clinical Development Leadership Team in Place

KINect® Platform

Proprietary Kinase Discovery Engine

- Versatile discovery platform
- Fully integrated discovery and development team
- Advancing small molecule drug candidates designed to parallel or exceed efficacy of high-value biologics

Innovative pipeline
(investigational drug candidates)

Zunsemetinib (ATI-450) - MK2i

- Oral anti-TNFα, anti-IL17, anti-IL1, anti-IL6

ATI-1777 - Topical "Soft" JAK1/3i

- Tissue specific therapy

ATI-2138 - ITK/JAK3i

- Oral dual inhibitor of T cell and cytokine receptors

Development of Small Molecule Therapeutics for Immuno-inflammatory Diseases

Note: KINect® is the registered trademark of Aclaris Therapeutics, Inc.

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The Kinase Opportunity
Unlocking the Potential of the Kinome

Medically Important and Productive Target Class

Oncology

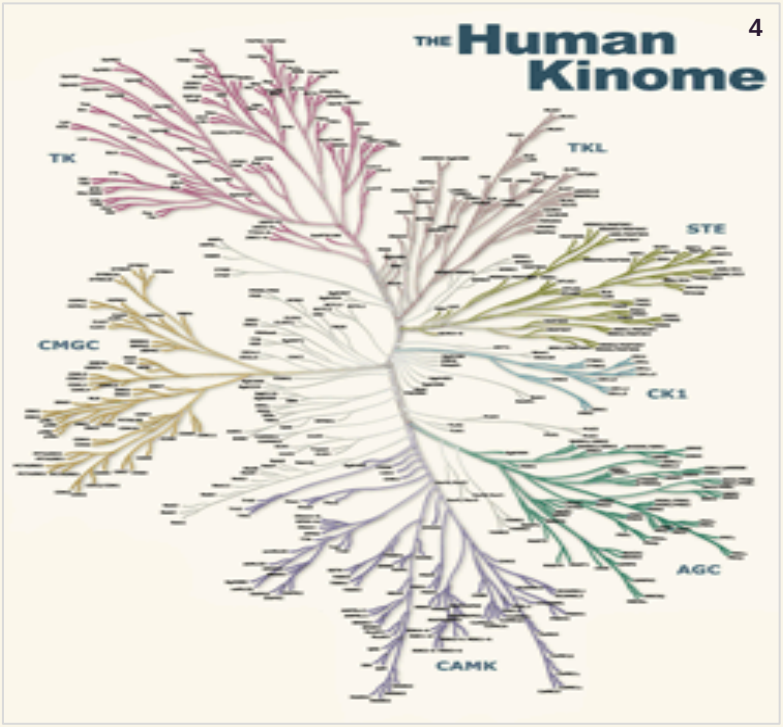
OFEV (nintedanib) capsules 150mg
IRESSA (gefitinib)
Bosulif (bosutinib)
IBRANCE (palbociclib)
ZELBORAF (vemurafenib) tablets
ICLUSIG (ponatinib) tablets
Inlyta (axitinib)
imbruvica (ibrutinib) 140mg capsules
gleevec (imatinib mesylate) tablets
GILOTRIF (afatinib) tablets
COMETRIQ (cabozantinib)
ICLUSIG (ponatinib) tablets 45mg, 15mg
Zydelig (idelalisib) tablets
SPRYCEL dasatinib
Votrient (pazopanib) tablets 200 mg
Jakafi (ruxolitinib) tablets
Mekinist (trametinib)
XALKORI (crizotinib)
Tykerb (lapatinib) 250mg tablets
Stivarga (regorafenib) tablets
Caprelsa (vandetanib) tablets
Nexavar (sorafenib) tablets
ZYKADIA ceritinib 150 mg capsules
SUTENT (sunitinib malate)
Tarceva (erlotinib)
LENVIMA (lenvatinib) capsules
Tasigna (nilotinib)

Non-Oncology

XELJANZ (tofacitinib citrate) 5mg tablets
RINVOQ upadacitinib 15mg tablets
olumiant (baricitinib) tablets 4mg, 2mg, 1mg
Opzelura (ruxolitinib) cream 1.5%
CIBINQO (abrocitinib) tablets
Jyseleca filgotinib 100 mg and 200 mg tablets
SOTYKTU (deucravacitinib) 6 mg tablets

>70 Marketed Drugs[1] ~$48B[2,3]
Annual Sales of Kinase Drugs

Most Members of the Kinome Remain Unexplored



518 Members
>90% of the Human Kinome remains undrugged[5]

Creating New Medicines Targeting Previously Inaccessible Kinome Targets

Note: All trademarks are the property of their respective owners.
1. GoodRx. Accessed January 4, 2023. https://www.goodrx.com/kinase-inhibitors; 2. Data on file; 3. Oprea TI, et al. Unexplored opportunities in the druggable human genome. Nature Rev Drug Discov. Poster Jan. 2017; 4. Manning G, et al. Science. 2002;298(5600):1912-1934; 5. Oprea TI, et al. Nat Rev Drug Discov. 2018;17(5):317-332.

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Precision Immunology with the KINect Platform
Demonstrated Success in Reversible and Covalent MOA

MK2 Inhibitors

- Zunsemetinib (ATI-450), ATI-2231: Oral anti-TNF, anti-IL17, anti-IL1, and anti-IL6
- Novel approach for a difficult to target kinase
- Broad potential in several immuno-inflammatory diseases

Unique kinase complex inhibitor

Tissue Restricted JAK Inhibitors

- ATI-1777: Skin specific (Soft) topical JAK1/3
- Oral Gut-biased JAK inhibitors
- Goal: Comparable clinical efficacy with improved safety profile

Tailoring physico-chemical and potency properties

Covalent ITK Inhibitors

- ATI-2138: ITK/JAK3 Oral T cell kinase inhibitor for autoimmune diseases

Covalent inhibition for difficult-to-target kinase

Small Molecule Therapeutics Targeting Multi-billion Dollar Immunology and Inflammation Markets

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Drug Development Pipeline

Drug Candidate / Program	Target	Route of Administration	Indication	Development Phase	Topline Data Expected
Immuno-Inflammatory Diseases					
Zunsemetinib (ATI-450)	MK2 inhibitor	Oral	Rheumatoid arthritis (moderate to severe)	Phase 2b	H2 2023
			Hidradenitis suppurativa (moderate to severe)	Phase 2a	Mid H1 2023
			Psoriatic arthritis (moderate to severe)	Phase 2a	YE 2023
ATI-1777	“Soft” JAK 1/3 inhibitor	Topical	Atopic dermatitis (moderate to severe)	Phase 2b	Mid 2023
ATI-2138	ITK/JAK3 inhibitor	Oral	T cell-mediated autoimmune diseases	Phase 1 Multiple Ascending Dose	H2 2023
Gut-Biased Program	JAK inhibitor	Oral	Inflammatory bowel disease	Discovery	
Oncology					
ATI-2231	MK2 inhibitor	Oral	Metastatic breast cancer	Preclinical	
			Pancreatic cancer		

Zunsemetinib (ATI-450): MK2 Inhibitor

(Investigational Drug Candidate)

Evolution in Understanding of a Well-Known Path

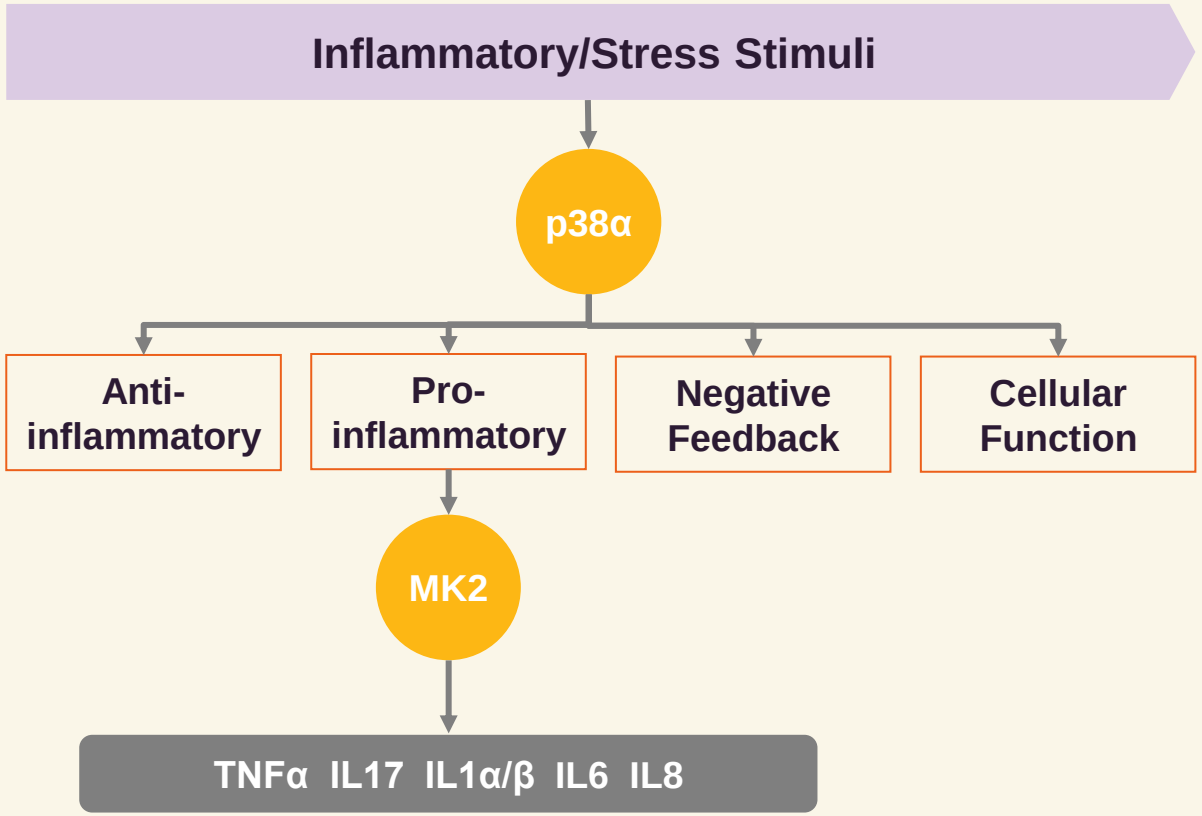
The Path From p38α to MK2

p38α was initially targeted for suppressing TNFα and other pro-inflammatory cytokines

Global p38α inhibitors have exhibited toxicity and/or lack of sustained efficacy "tachyphylaxis" in RA and IBD

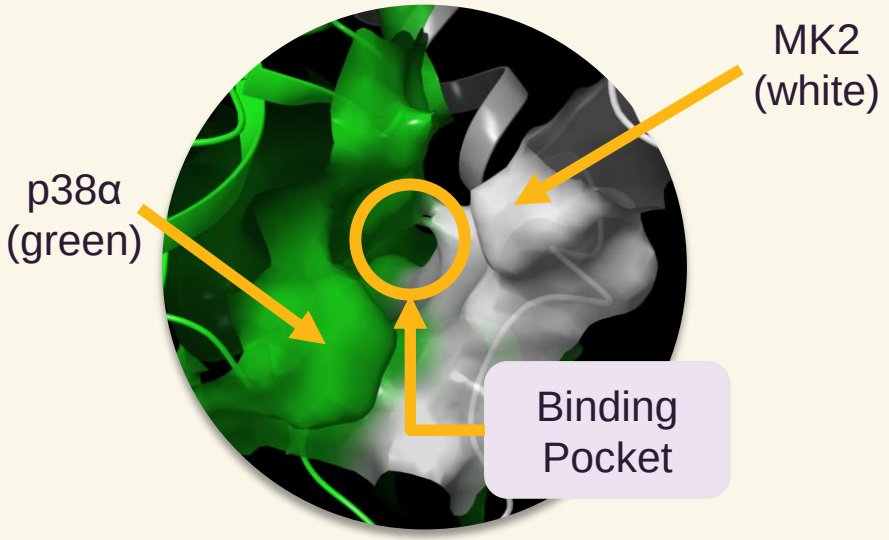
p38α phosphorylates over 60 substrates — yet MK2 drives the pro-inflammatory node of this pathway

MK2 has been a high priority therapeutic target since 1999 but has proven very difficult to drug

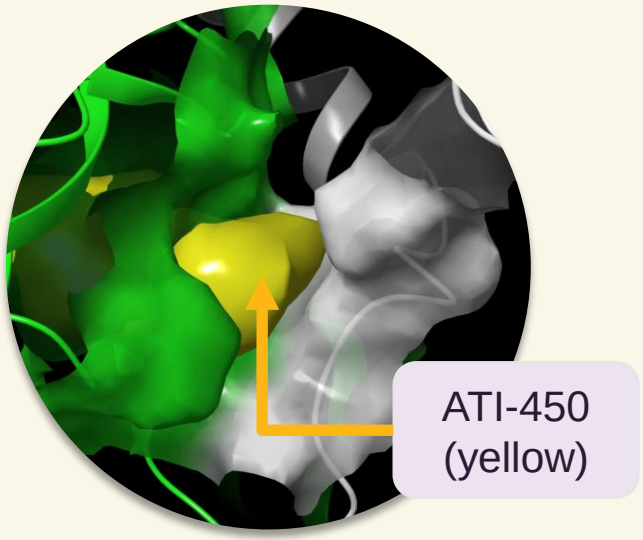


Note: Wang C, et al. J Exp Med. 2018;215(5):1315-1325; Cheung P, et al. EMBO J. 2003;22(21):5793-5805; Muniyappa H, et al. Cell Signal. 2008;20(4):675–683;. Ma W, et al. J Biol Chem. 2001;276(17):13664-13674.

Novel Mechanism: Locking MK2 in an Inactive State



Crystal structure of the p38α/MK2 complex



Zunsemetinib (yellow) docked in the pocket

- In the nucleus, inactive MK2 and p38α dock in a high affinity complex that generates a binding pocket formed by juxtaposed walls of both proteins
- Zunsemetinib binds to both walls of the pocket, stabilizing the complex and preventing MK2 activation

Zunsemetinib locks MK2 in a catalytically inactive state – a unique MOA

Note: Wang C, et al. J Exp Med. 2018;215(5):1315-1325.

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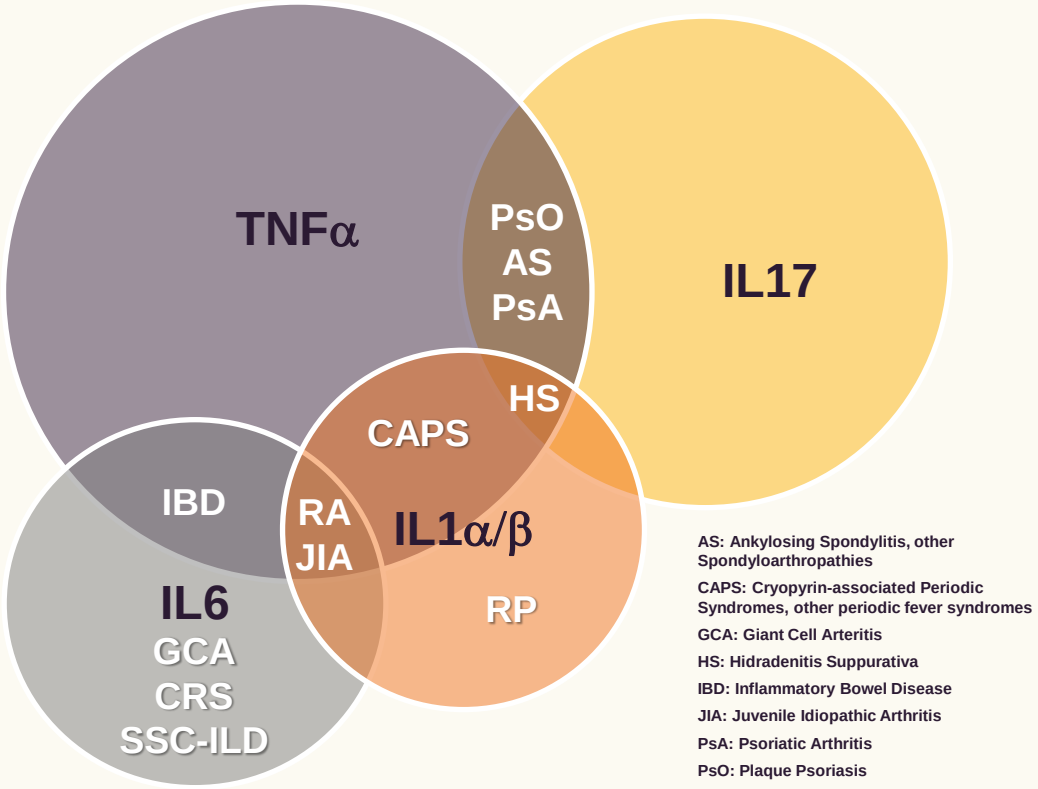
Zunsemetinib: Investigational Small Molecule, Oral MK2 Inhibitor
Designed to Block the Targets of Broadly-Used Biologics

Inhibiting MK2 blocks TNFα, IL17, IL1α/β and IL6[1], the targets of commercially successful biologics



AS: Ankylosing Spondylitis, other Spondyloarthropathies
CAPS: Cryopyrin-associated Periodic Syndromes, other periodic fever syndromes
GCA: Giant Cell Arteritis
HS: Hidradenitis Suppurativa
IBD: Inflammatory Bowel Disease
JIA: Juvenile Idiopathic Arthritis
PsA: Psoriatic Arthritis
PsO: Plaque Psoriasis
RA: Rheumatoid Arthritis
RP: Recurrent Pericarditis
SSc-ILD: Scleroderma-associated interstitial lung disease

MK2 drives pro-inflammatory cytokine expression

By inhibiting multiple cytokines, zunsemetinib may be a potential treatment for multiple diseases

Potential alternative to injectable, anti-cytokine biologics and JAK inhibitors for immuno-inflammatory diseases

Global immunology market valued at >$97B in 2021[2]

1. Data on file; 2. Fortune Business Insights. Accessed January 4, 2023. https://www.fortunebusinessinsights.com/industry-reports/immunology-market-100657;

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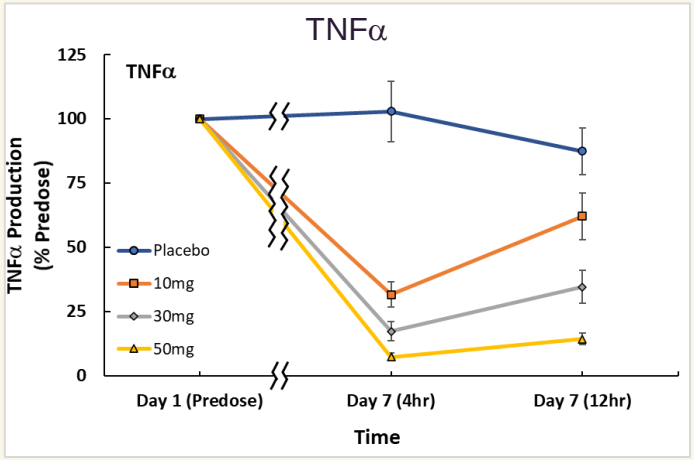
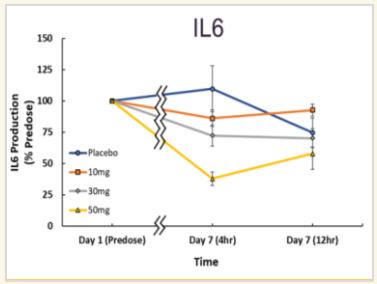
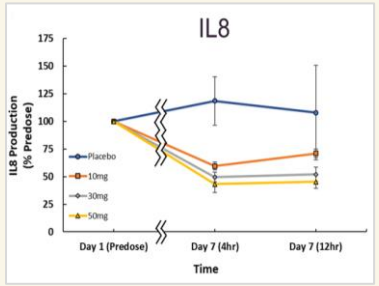
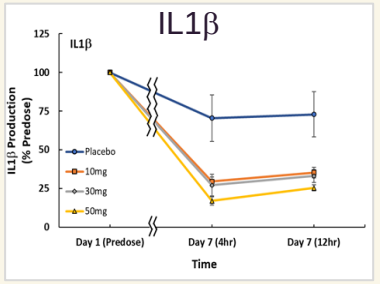
Zunsemetinib Demonstrated Strong Inhibition Across Key Cytokines

Zunsemetinib dosed orally BID for 7 days in healthy subjects at doses of 10, 30 or 50 mg in Phase 1

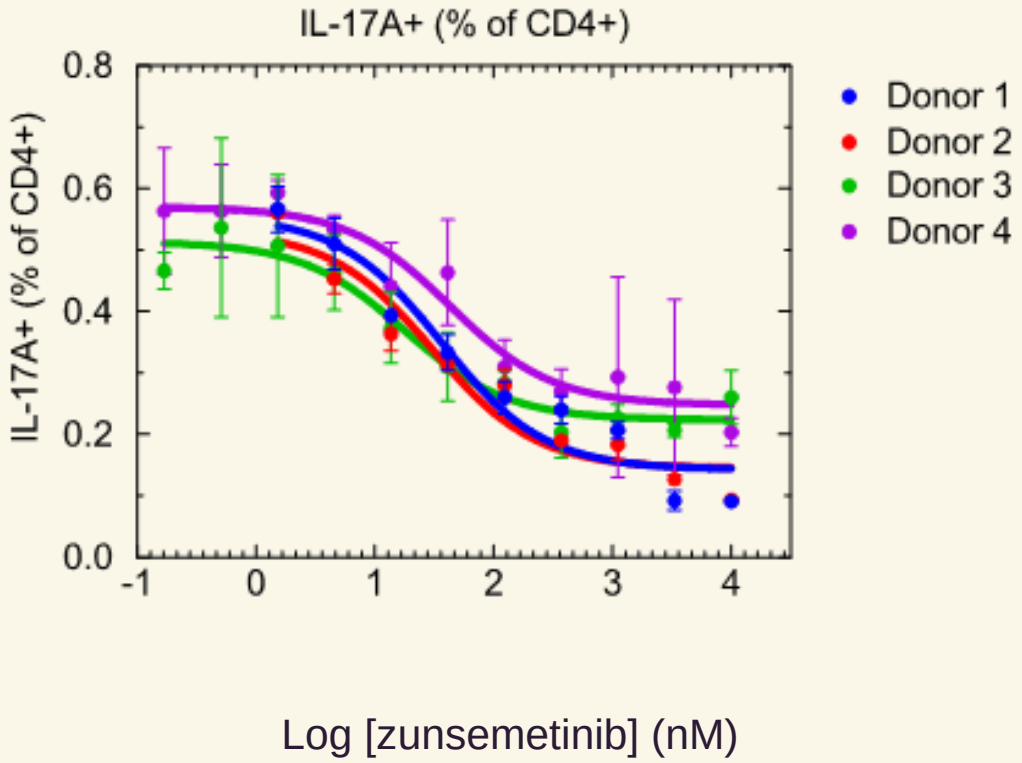








hPBMC treated with antiCD3/28 for 72 hr in-vitro



Note: Data on file

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Zunsemetinib Phase 2a Trial in Rheumatoid Arthritis
Summary of Clinical Data

Potent and Durable Clinical Efficacy with 50mg

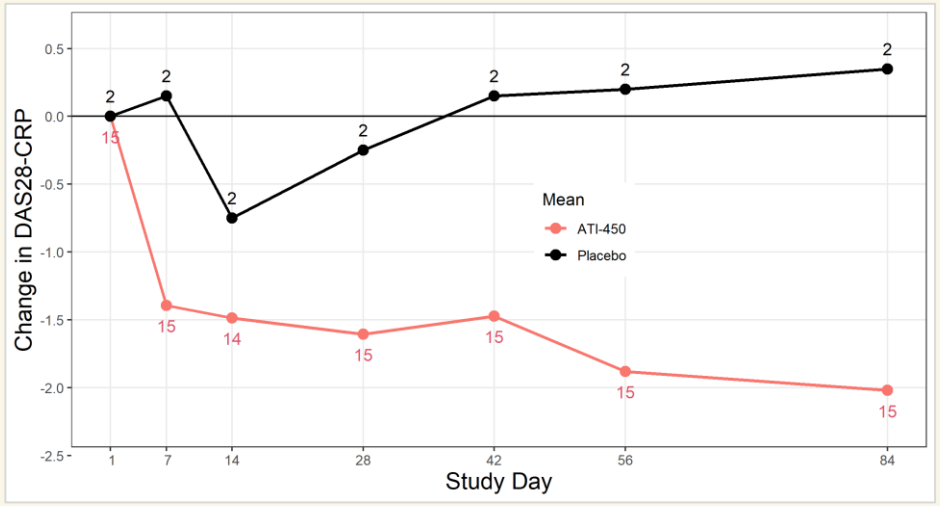
Main Objectives of POC Study were addressed

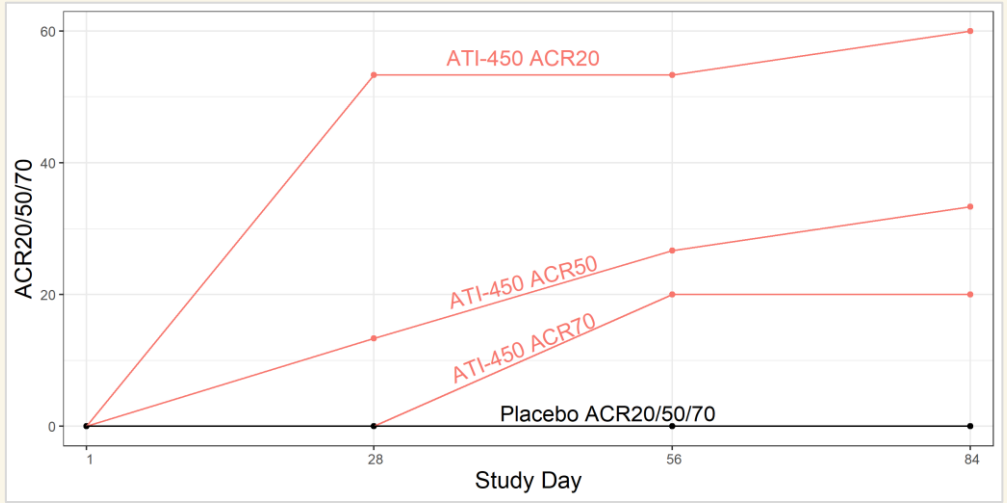
Potent and durable clinical efficacy with 50mg BID:

- DAS-28-CRP reduction persisted
- ACR effect comparable to other mechanisms
- hsCRP reduction maintained

Zunsemetinib was generally well tolerated

Summary of Efficacy Endpoints





On-Going Phase 2 Studies: Zunsemetinib

Hidradenitis Suppurativa 12-week phase 2a randomized trial	Rheumatoid Arthritis 12-week phase 2b randomized trial	Psoriatic Arthritis 12-week phase 2a randomized trial
Trial size: 95 subjects	Trial size: 240 subjects	Trial size: 70 subjects
Dose arms: Randomized 1:1 to Zunsemetinib 50 mg BID and placebo	Dose arms: Randomized 1:1:1 to Zunsemetinib 50 mg BID, 20 mg BID and placebo	Dose arms: Randomized 1:1 to Zunsemetinib 50 mg BID and placebo
Entry criteria: Moderate-severe HS	Entry criteria: Moderate-severe RA on methotrexate	Entry criteria: Moderate-severe PsA unresponsive to ≥ 1 non-biologic DMARD
Expected Topline Data: Mid-1H 2023	Expected Topline Data: 2H 2023	Expected Topline Data: YE 2023

ATI-1777 (Topical “Soft” JAK Inhibitor)

(Investigational Drug Candidate)

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Aiming to Develop an Effective and Safe Therapy for Atopic Dermatitis

Atopic dermatitis (AD) is a chronic, pruritic inflammatory skin condition[1]

- The U.S. prevalence of AD is reported to be 11.3–12.7% in children and 6.9–7.6% in adults[2]
- Market projected to be $8-12 billion at peak (moderate to severe AD)[3]
- Systemic and topical JAK inhibition has demonstrated promising results in AD clinical trials[4]

Goal

- Comparable efficacy to other topical JAKs but a “soft” drug to minimize the potential for systemic toxicities
- JAK1/3 selective to minimize JAK2 mediated hematopoietic effects
- Patients with moderate to severe AD
- Deliver in a patient-friendly formulation

ATI-1777 (investigational compound)

- First-in-human Phase 2a trial in subjects with moderate to severe AD completed
- 4-week trial in subjects with moderate to severe AD completed with primary endpoint of % change from baseline in mEASI
- Phase 2b dose ranging study underway

1. Medscape. Accessed January 7, 2023. https://emedicine.medscape.com/article/1049085-overview. 2. Silverberg J. Dermatol Clin. 2017;Jul;35(3):283-289; 3. Auster M, et al. Something Big Is Getting Bigger [research note]. Credit Suisse Equity Research; 2019; 4. Shreberk-Hassidim R, et al. J Am Acad Dermatol. 2017;Apr;76(4):745-753.

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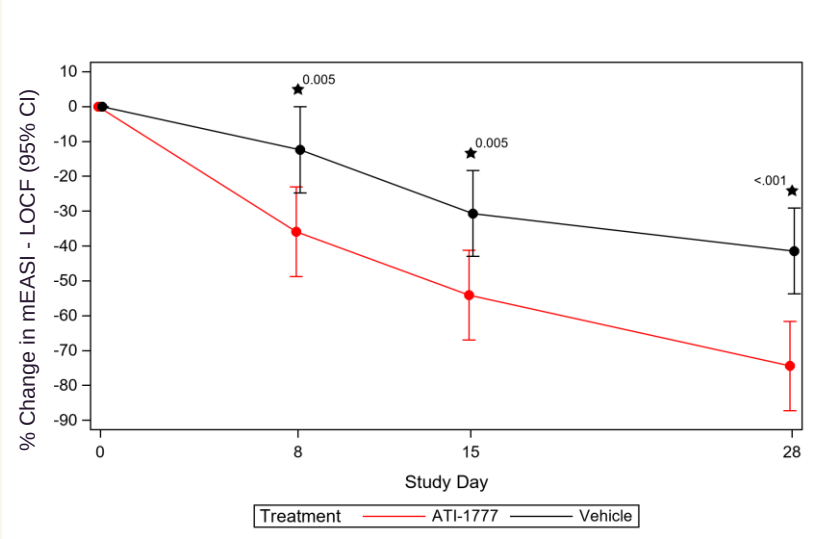
Positive Data Demonstrated in ATI-1777 Phase 2 Study in Atopic Dermatitis

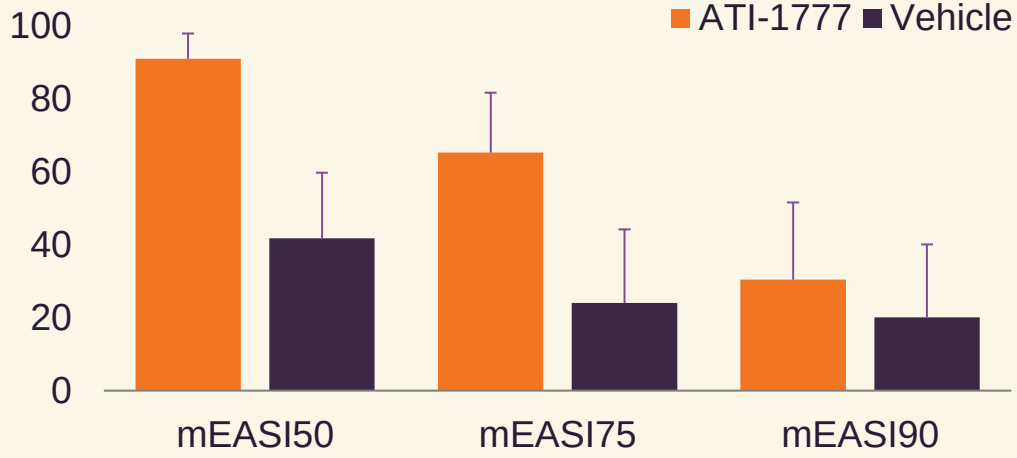
Phase 2a Trial Highlights

- ATI-1777 achieved statistically significant result in the primary efficacy endpoint at week 4
- Positive trends were observed in secondary endpoints including improvement of itch, percent of mEASI-50 responders, IGA responder analysis and reduction in BSA impacted by disease
- ATI-1777 was generally well tolerated

Primary Efficacy Endpoint: % Change in mEASI – LOCF (FAS)



Secondary Efficacy Endpoint: mEASI50/75/90 at Day 28 (FAS)



Note: (FAS): Full Analysis Set

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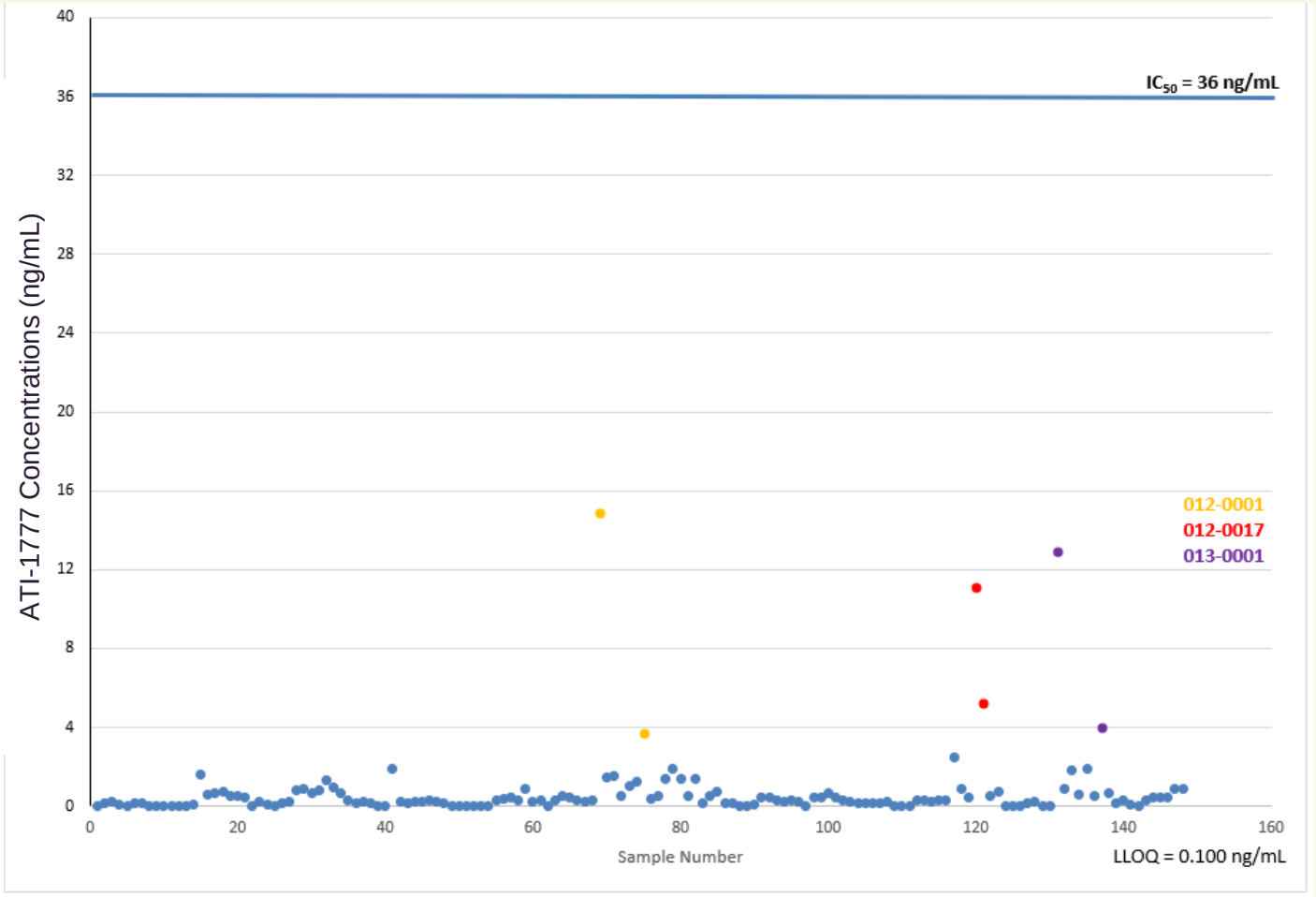
Low Plasma Levels of ATI-1777 Following Topical Application

PK Plasma Concentrations of ATI-1777 in Subjects



- All concentrations < ½ IC_{50} (IC_{50} = 36 ng/mL for JAK1/3)
- >86% of samples tested following ATI-1777 administration exhibited blood levels below the detectable level
- Average concentration in subjects receiving ATI-1777 solution was never >5% the IC_{50}
- Only 3 subjects (6 out of 148 total samples) with concentrations > 1/10th the IC_{50}

Note: Data on file

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ATI-1777 Status

Positive Proof of Concept First in Human Study

- Moderate to Severe Atopic Dermatitis
  - ✓ Traditionally the domain of systemic therapy
- Rapid and continuing improvement over 4 weeks
- PK supports lack of systemic drug penetration
- Generally, well tolerated

Potential Positioning in Moderate to Severe Atopic Dermatitis

- Monotherapy
- Combination therapy with biologics to potentially drive improved efficacy[1]

Licensing Agreement with Pediatrix Therapeutics for Greater China

Phase 2b Data Upcoming in Atopic Dermatitis (Expected Mid-Year 2023)

1. Reich, Teixeira, Bruin-Weller, Bieber, Lancet 397, Issue 10290, P2169-2181, June 5, 2021
Note: Data on file

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ATI-2138 (ITK/JAK3 Inhibitor)

(Investigational Drug Candidate)

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

Background

- ATI-2138 covalently blocks ITK/JAK3[1]
  - ✓ Potential for synergistic efficacy
    - ITK required for T cell receptor (TCR) signaling
    - JAK3 required for IL2Rγ common cytokines (IL-2/4/7/9/15/21)
- JAK3 is the only JAK that is inhibited
- Tissue restricted expression could enhance safety
- ATI-2138 is selective for T cell signaling[2,3]
- 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
- Phase 1 Multiple Ascending Dose Study initiated
- 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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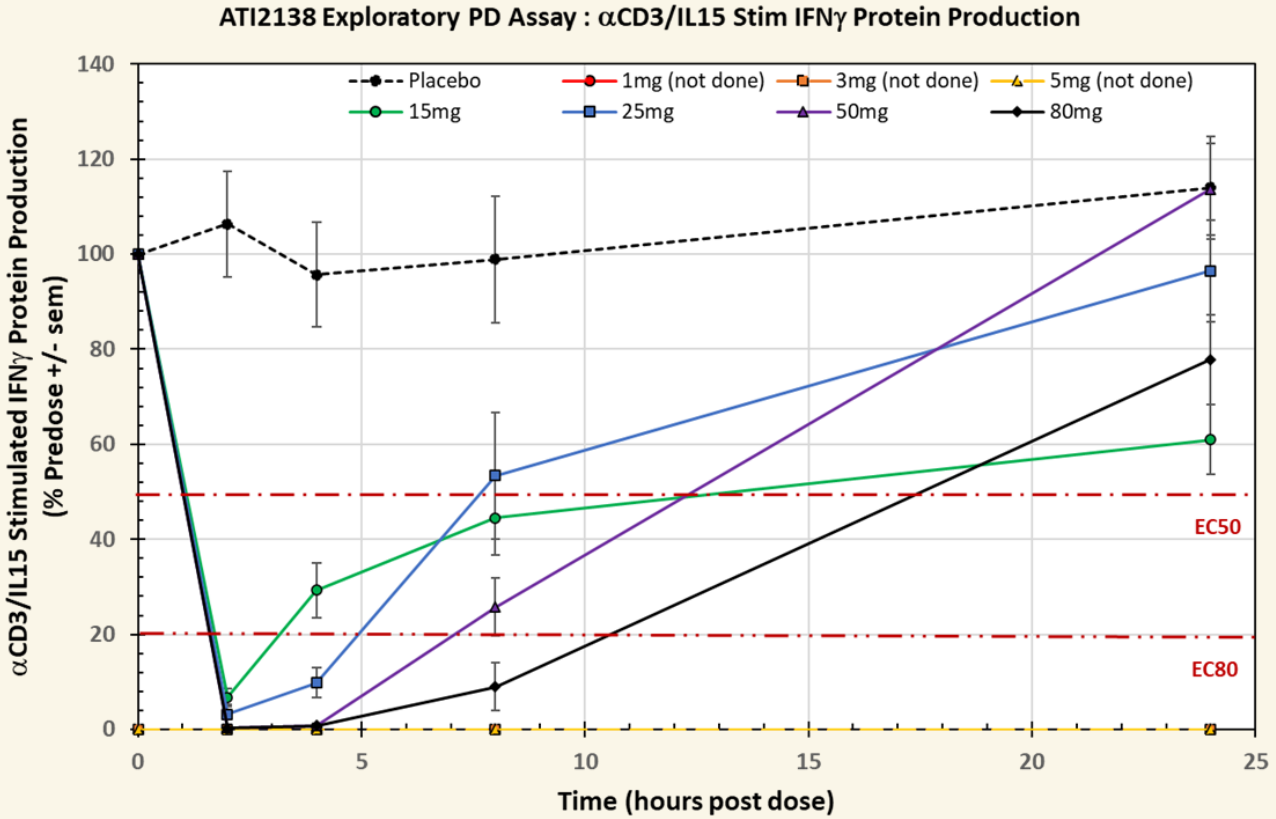
Simultaneous Stimulation of the ITK and JAK3 Pathways was Dose-Dependently Inhibited by ATI-2138

Phase 1 SAD Trial Highlights

- Safety Profile
  - ✓ ATI-2138 was generally well tolerated at all doses tested in the trial up to 80mg single dose
- PK
  - ✓ The PK data demonstrated dose-dependent exposure
  - ✓ Terminal half-life ranged from 1.5 – 2.5 hours
- PD
  - ✓ Dose-dependent inhibition of both ITK and JAK3 exploratory PD biomarkers was observed

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

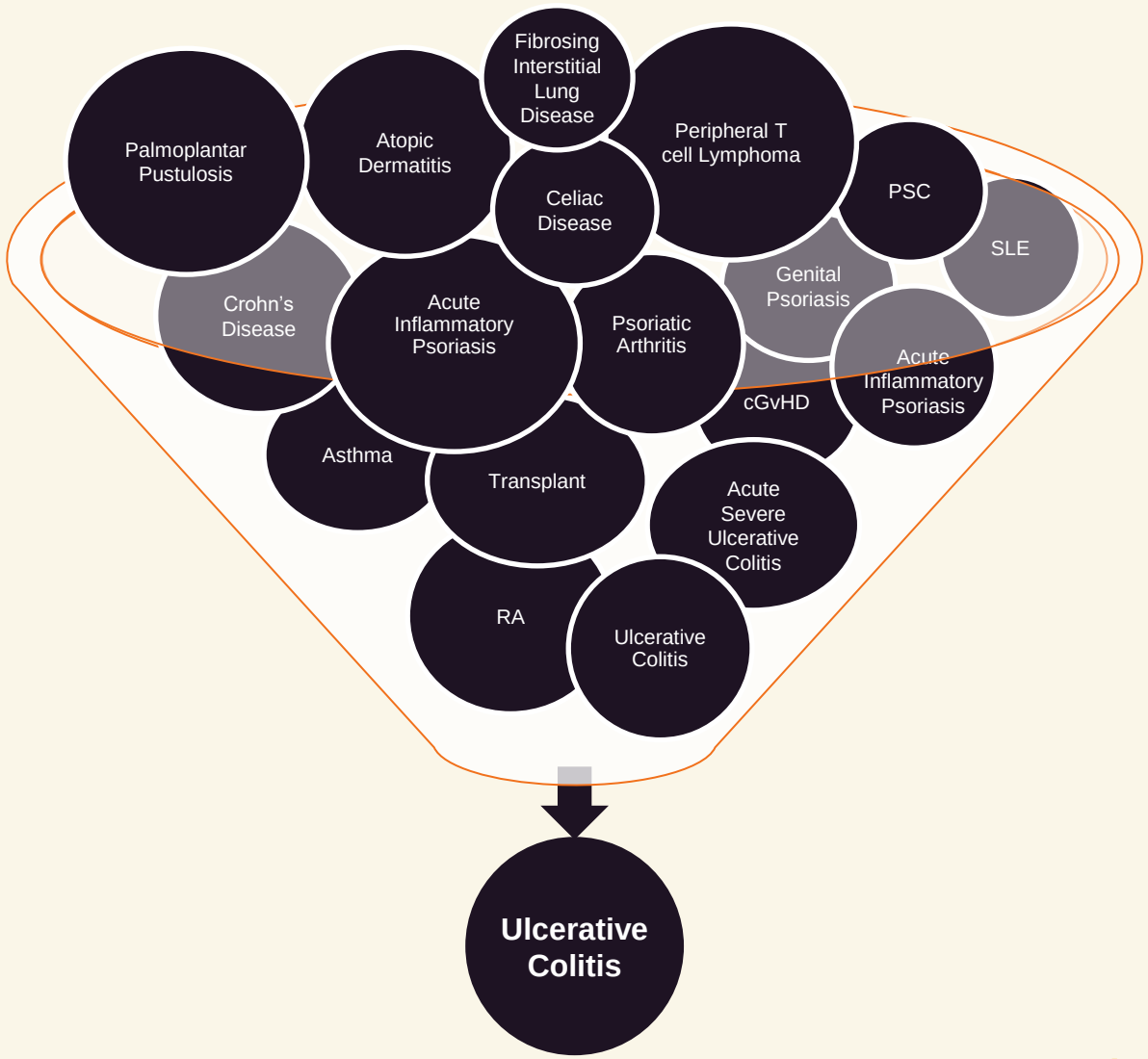


Pharmacodynamic Dual Stimulation Assay

Wide Array of Disease Targets for ATI-2138

Ulcerative Colitis Selected as First Indication for Proof of Concept

- Genetic linkage of the ITK locus to a murine model of disease[1]
- Elevated expression of ITK in colonic mucosa of UC patients[1]
- Similar T cell signaling of pathway of cyclosplorine, a successful treatment for US that bears significant toxicity risks
- Continued need for new treatment approaches in UC, with increasing incidence and prevalence expected in the future[2]



1. Gastroenterology 2021; 161:1270-87; 2. Lancet GI&Hep, 2020. 5(1)17-30.

Corporate Highlights

Empowering Patients Through Kinome Innovation

Executive Team

Proven track record of R&D, business development and scientific leadership in immuno-inflammatory diseases

KINect Technology Platform

Proprietary discovery engine enables targeted design of novel drug candidates

Pipeline

Multiple therapeutic programs ranging from discovery to clinical development

Intellectual Property

Global IP estate

Financial Strength

Ended Q3 2022 with $248M of cash, cash equivalents and marketable securities and cash runway expected through end of 2025

Commitment to Patients

Focus on addressing the needs of patients with immuno-inflammatory diseases who lack satisfactory treatment options

Experienced Leadership Team

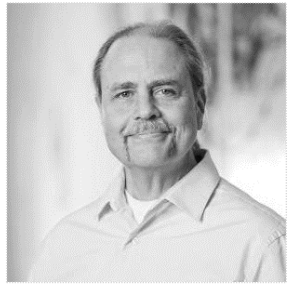
Douglas Manion
Chief Executive Officer

Over 25 years Pharmaceutical Industry Experience

Former EVP of R&D at Arena Pharmaceuticals

Former CEO of Kleo Pharmaceuticals

Former R&D leadership roles at BMS, GSK and DuPont Pharmaceuticals



Joseph Monahan
Chief Scientific Officer

Over 35 years pharmaceutical research experience

Lead Founder and Former CSO of Confluence Life Sciences

Former Pfizer Leader of Global Kinase Team

> 100 publications and patents (>30 total on kinases)

Matthew Rothman
General Counsel

Over a decade of legal leadership experience

Former corporate and securities group associate at Dechert LLP

Gail Cawkwell
Chief Medical Officer

Pediatric rheumatologist and epidemiologist with over 20 years of pharmaceutical development and medical affairs experience

Former SVP of Medical Affairs and Safety at Intercept Pharmaceuticals

Former leadership roles at Pfizer and other pharmaceutical companies

Kevin Balthaser
Chief Financial Officer

Over 13 years of financial leadership including 10 years in the pharmaceutical industry

Former accounting and finance roles at Lannett Company, Inc. and Pricewaterhouse Coopers, LLP.

Certified Public Accountant

James Loerop
Chief Business Officer

Over 30 years of large pharma and biotech business development experience

Former EVP of BD and Strategic Planning at Anika Therapeutics

Former Business Development leadership roles at Alexion, GSK and Stifel Laboratories

Drug Development Pipeline

Drug Candidate / Program	Target	Route of Administration	Indication	Partner	Development Phase
Immuno-Inflammatory Diseases					
Zunsemetinib (ATI-450)	MK2 inhibitor	Oral	Rheumatoid arthritis (moderate to severe)		Phase 2b
			Hidradenitis suppurativa (moderate to severe)		Phase 2a
			Psoriatic arthritis (moderate to severe)		Phase 2a
ATI-1777	"Soft" JAK 1/3 inhibitor	Topical	Atopic dermatitis (moderate to severe)	Pediatrix Therapeutics 祐儿医药	Phase 2b
ATI-2138	ITK/JAK3 inhibitor	Oral	T cell-mediated autoimmune diseases		Phase 1
Gut-Biased Program	JAK inhibitor	Oral	Inflammatory bowel disease		Discovery
Oncology					
ATI-2231	MK2 inhibitor	Oral	Metastatic breast cancer		Preclinical
			Pancreatic cancer		

Note 1: In November 2022, Aclaris Therapeutics and Pediatrix Therapeutics Announced a License Agreement for ATI-1777 in Greater China
2: All trademarks are the property of their respective owners.

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2023 Expected Data Readouts