

EMPOWERING PATIENTS THROUGH KINOME INNOVATION

Corporate Overview

February 2023



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,” “intend,” “may,” “plan,” “potential,” “will,” and similar expressions, and are based on Aclaris’ current beliefs and expectations. These forward-looking statements include expectations regarding the development of Aclaris’ drug candidates, including the timing of its clinical trials, availability of data from those trials, and regulatory filings, identification of novel development candidates through Aclaris’ KINect discovery engine, and its belief that its existing cash, cash equivalents and marketable securities will be sufficient to fund its operations through the end of 2025. 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, Aclaris’ ability to enter into strategic partnerships on commercially reasonable terms, the uncertainty regarding the macroeconomic environment and the COVID-19 pandemic 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, 2022, 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 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.

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-TNF α , 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.

The Kinase Opportunity

Unlocking the Potential of the Kinome

Medically Important and Productive Target Class

Oncology

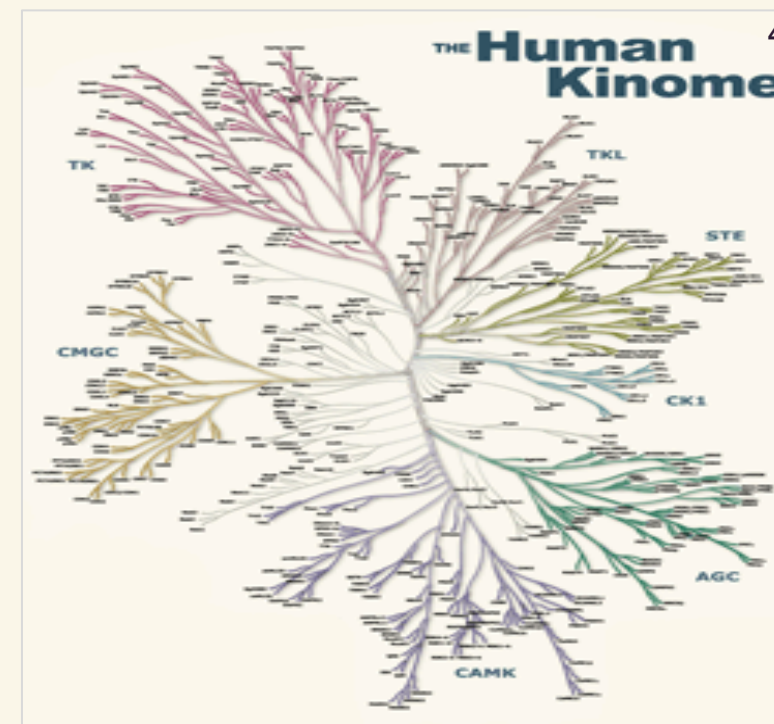


Non-Oncology



>70 Marketed Drugs¹ ~\$48B^{2,3}
Annual Sales of Kinase Drugs

Most Members of the Kinome Remain Unexplored



518 Members
>90% of the Human Kinome remains undrugged⁵

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.

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

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	March 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 p38 α to MK2

p38 α was initially targeted for suppressing TNF α and other pro-inflammatory cytokines



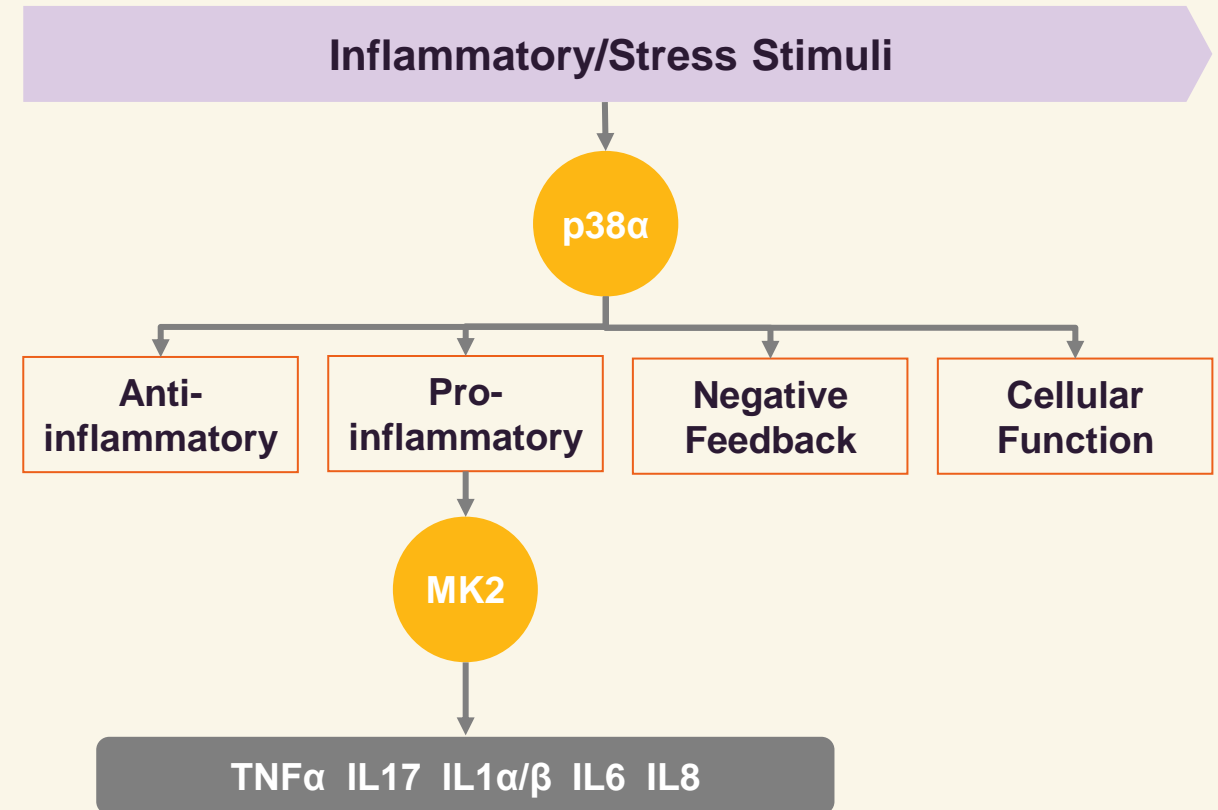
Global p38 α inhibitors have exhibited toxicity and/or lack of sustained efficacy “tachyphylaxis” in RA and IBD



p38 α phosphorylates over 60 substrates — yet MK2 drives the pro-inflammatory node of this pathway

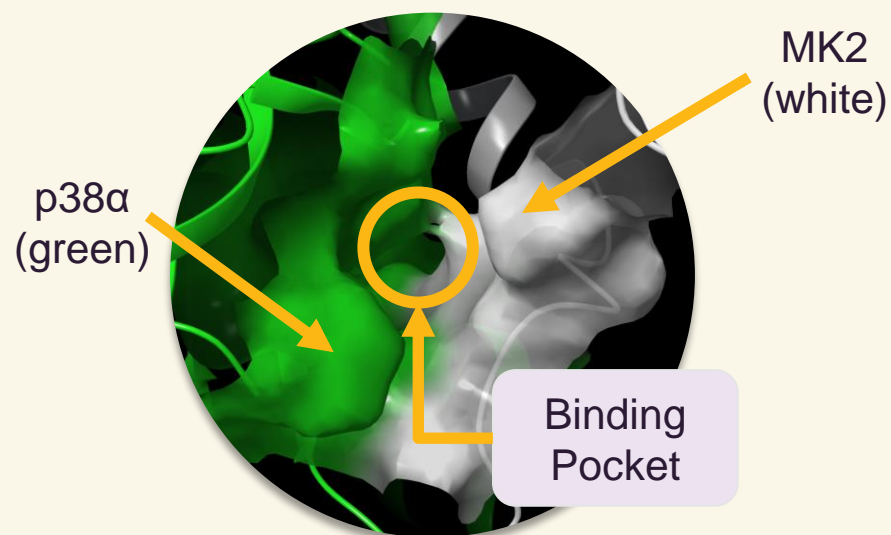


MK2 has been a high priority therapeutic target since 1999 but has proven very difficult to drug

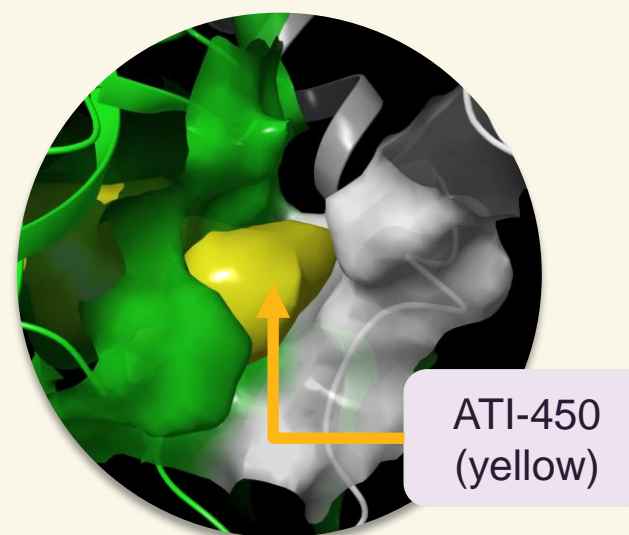


Note: Wang C, et al. J Exp Med. 2018;215(5):1315-1325; Cheung P, et al. EMBO J. 2003;22(21):5793-5805; Muniyappa H, et al. Cell Signal. 2008;20(4):675–683; Ma W, et al. J Biol Chem. 2001;276(17):13664-13674.

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

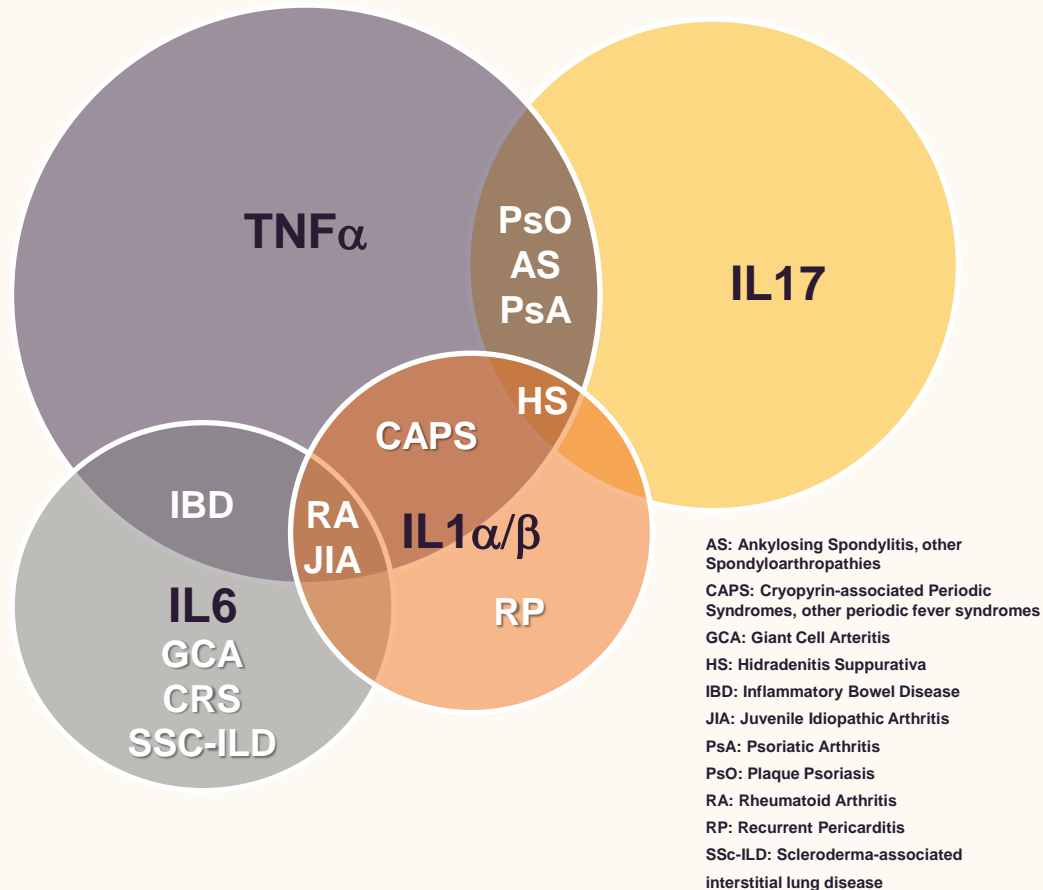
Zunsemetinib locks MK2 in a catalytically inactive state – a unique MOA

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

Zunsemetinib: Investigational Small Molecule, Oral MK2 Inhibitor

Designed to Block the Targets of Broadly-Used Biologics

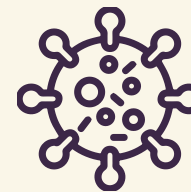
Inhibiting MK2 blocks $\text{TNF}\alpha$, IL17, IL1 α/β and IL6¹, the targets of commercially successful biologics



MK2 drives pro-inflammatory cytokine expression



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



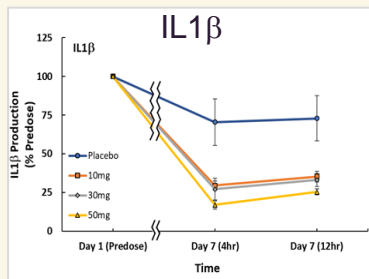
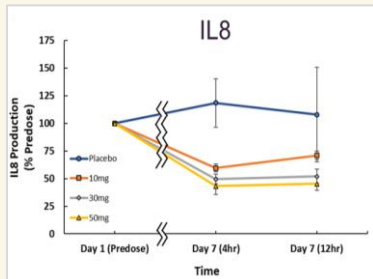
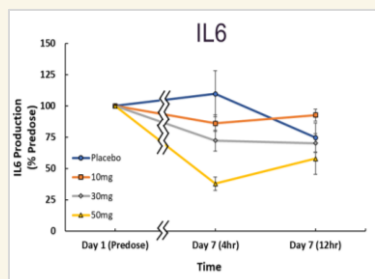
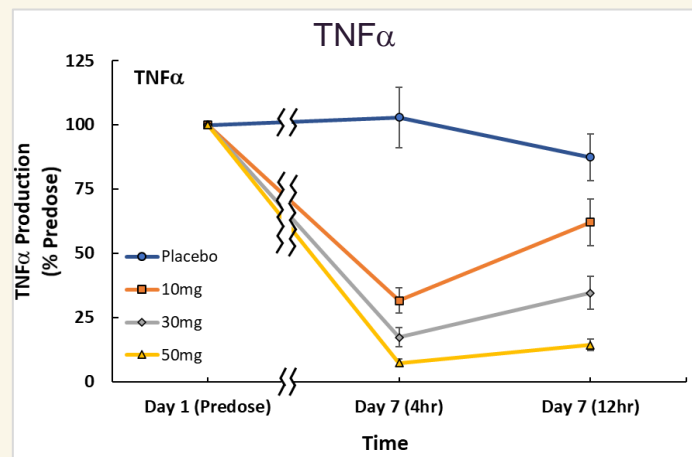
Potential alternative to injectable, anti-cytokine biologics and JAK inhibitors for immuno-inflammatory diseases

Global immunology market valued at >\$97B in 2021²

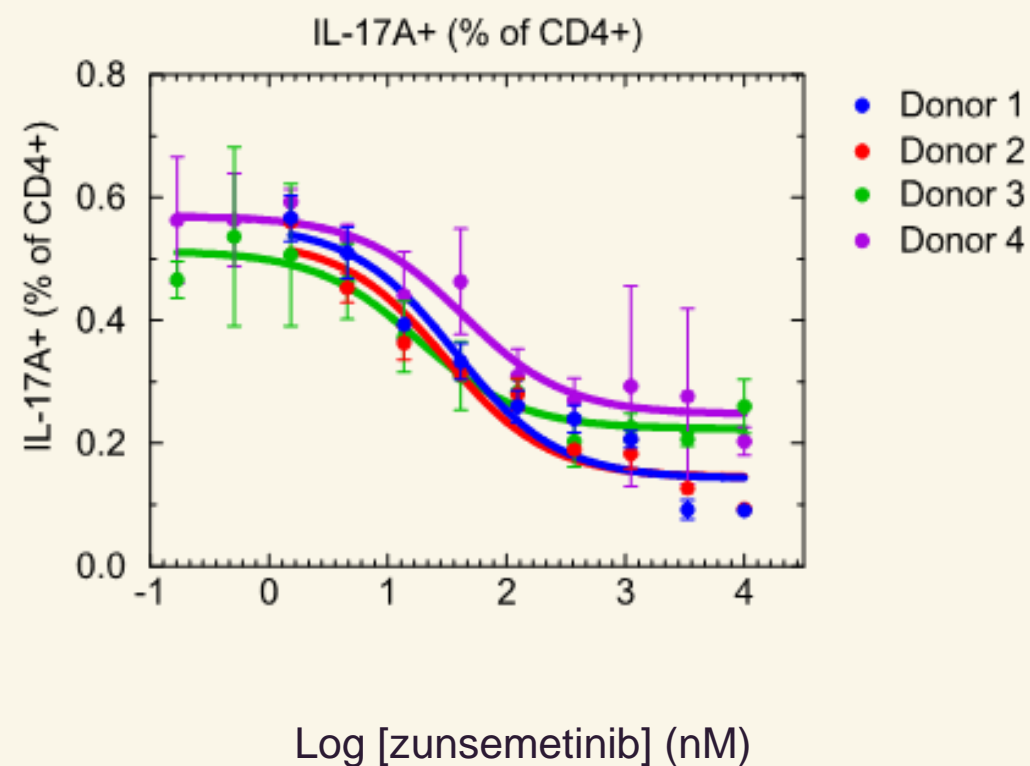
1. Data on file; 2. Fortune Business Insights. Accessed January 4, 2023. <https://www.fortunebusinessinsights.com/industry-reports/immunology-market-100657>;

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

Zunsemetinib Phase 2a Trial in Rheumatoid Arthritis

Summary of Clinical Data

**Potent and
Durable
Clinical
Efficacy
with 50mg**

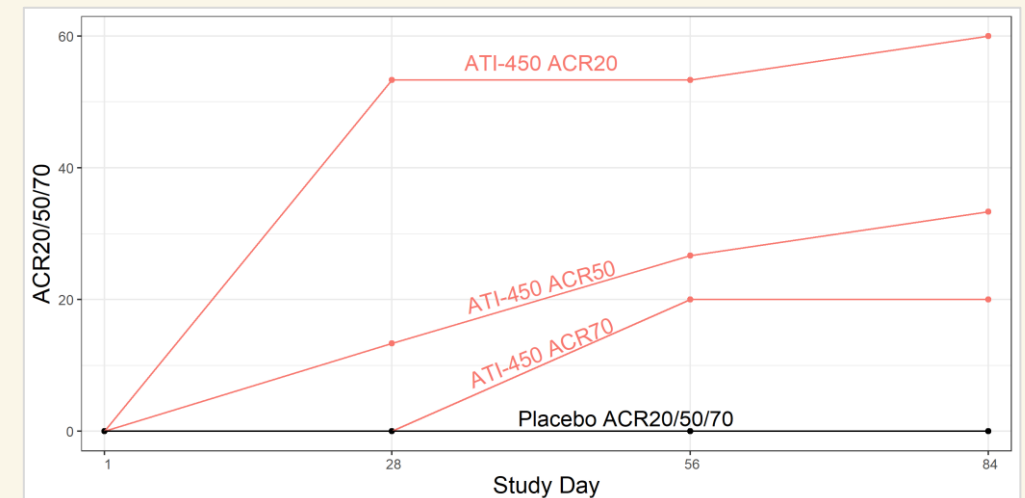
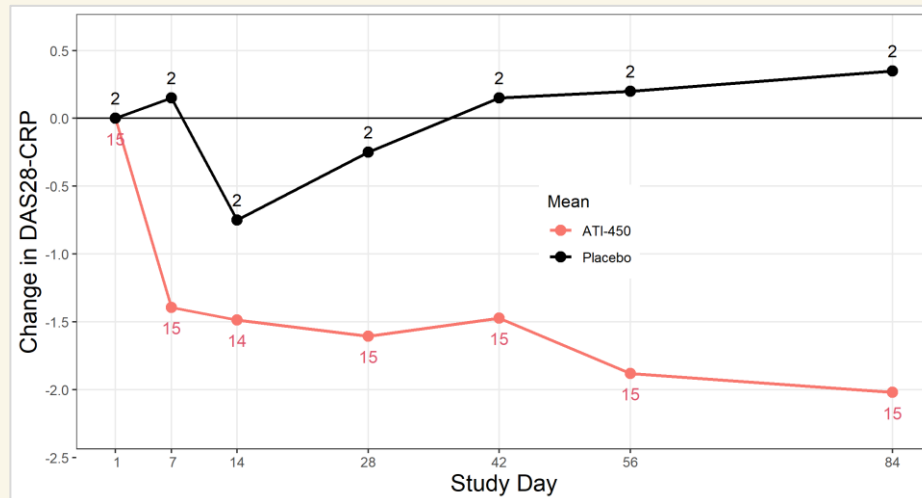
Main Objectives of POC Study were addressed

Potent and durable clinical efficacy with 50mg BID:

Zunsemetinib was generally well tolerated

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

**Summary of
Efficacy
Endpoints**



On-Going Phase 2 Studies: Zunsemetinib

Hidradenitis Suppurativa 12-week phase 2a randomized trial

Trial size: 95 subjects

Dose arms: Randomized 1:1 to
Zunsemetinib 50 mg BID
and placebo

Entry criteria:
Moderate-severe HS

Expected Topline Data:
March 2023

Rheumatoid Arthritis 12-week phase 2b randomized trial

Trial size: 240 subjects

Dose arms: Randomized 1:1:1
to Zunsemetinib 50 mg BID, 20
mg BID and placebo

Entry criteria: Moderate-severe
RA on methotrexate

Expected Topline Data:
2H 2023

Psoriatic Arthritis 12-week phase 2a randomized trial

Trial size: 70 subjects

Dose arms: Randomized 1:1 to
Zunsemetinib 50 mg BID
and placebo

Entry criteria: Moderate-severe
PsA unresponsive to ≥ 1 non-
biologic DMARD

Expected Topline Data:
YE 2023

ATI-1777 (Topical “Soft” JAK Inhibitor)

(Investigational Drug Candidate)



Aiming to Develop an Effective and Safe Therapy for Atopic Dermatitis

Atopic dermatitis (AD) is a chronic, pruritic inflammatory skin condition¹

- The U.S. prevalence of AD is reported to be 11.3–12.7% in children and 6.9–7.6% in adults²
- 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 trials⁴

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

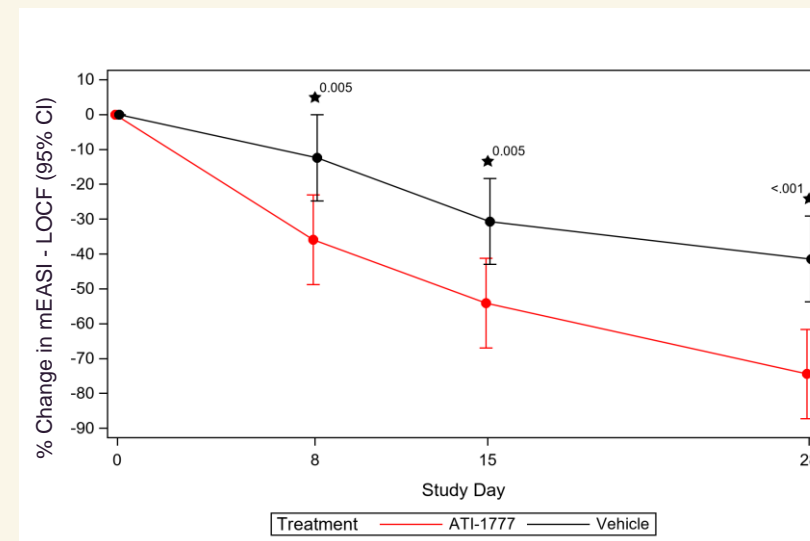
1. Medscape. Accessed January 7, 2023. <https://emedicine.medscape.com/article/1049085-overview>. 2. Silverberg J. Dermatol Clin. 2017;Jul;35(3):283-289; 3. Auster M, et al. Something Big Is Getting Bigger [research note]. Credit Suisse Equity Research; 2019; 4. Shreberk-Hassidim R, et al. J Am Acad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

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

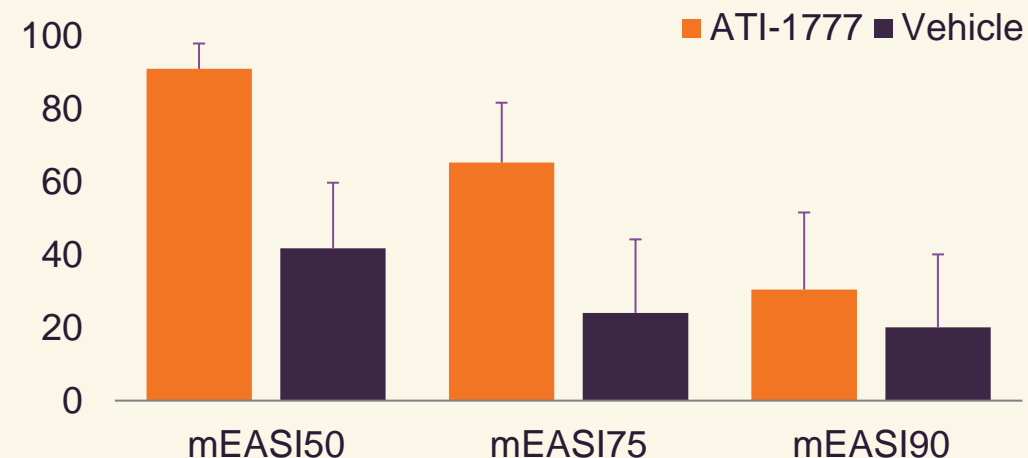
Phase 2a Trial Highlights

- 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)



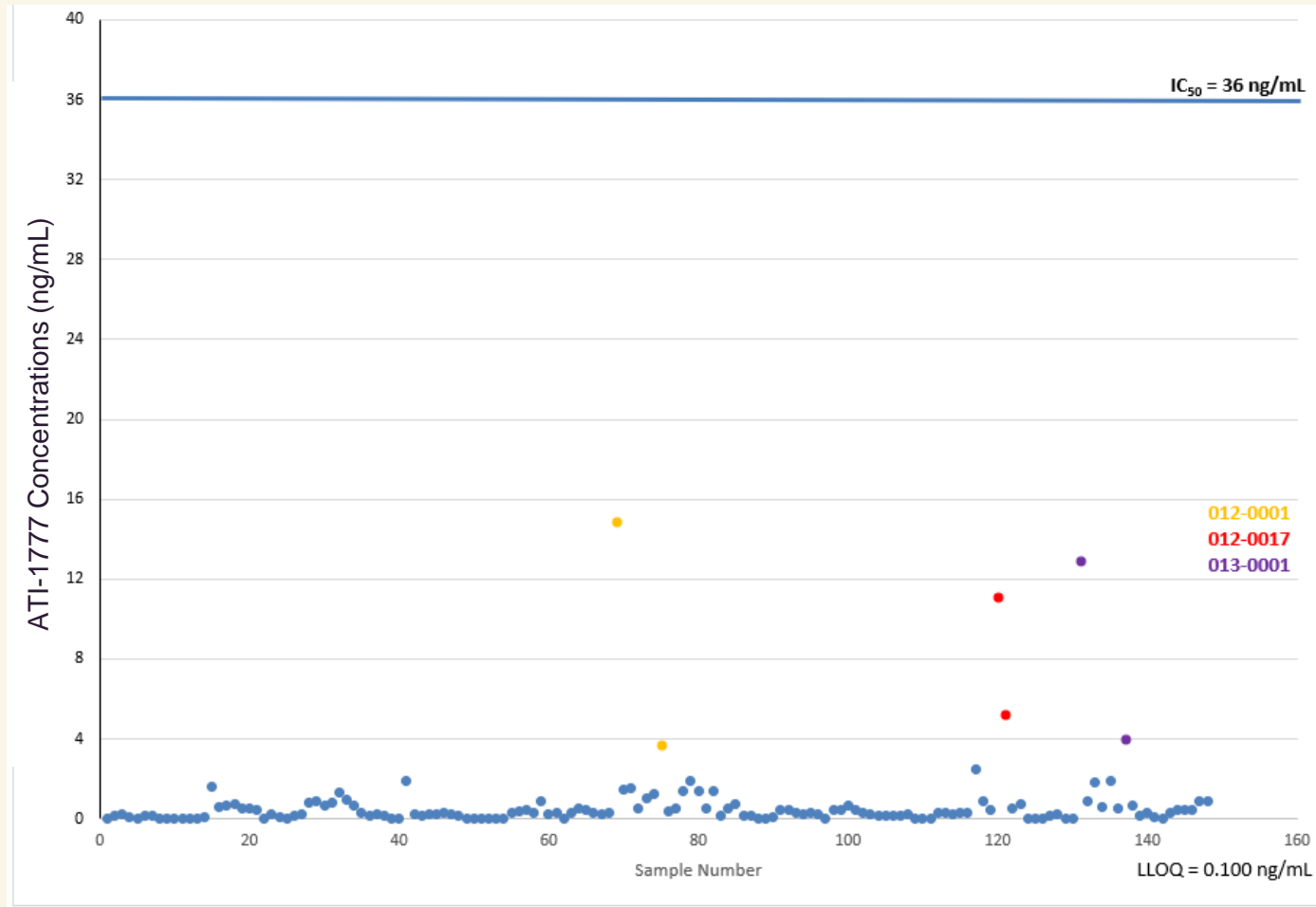
Secondary Efficacy Endpoint:
mEASI50/75/90 at Day 28 (FAS)



Note: (FAS): Full Analysis Set

Low Plasma Levels of ATI-1777 Following Topical Application

PK Plasma Concentrations of ATI-1777 in Subjects



Note: Data on file

- All concentrations $< \frac{1}{2} \text{IC}_{50}$ ($\text{IC}_{50} = 36 \text{ ng/mL}$ 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 $> 1/10^{\text{th}}$ the IC_{50}

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 efficacy¹



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

ATI-2138 (ITK/JAK3 Inhibitor)

(Investigational Drug Candidate)



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

Background



- ATI-2138 covalently blocks ITK/JAK3¹
 - ✓ Potential for synergistic efficacy
 - ITK required for T cell receptor (TCR) signaling
 - JAK3 required for IL2R γ 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
- Phase 1 Multiple Ascending Dose Study initiated
- Phase 2a Proof of Concept study in Ulcerative Colitis under development

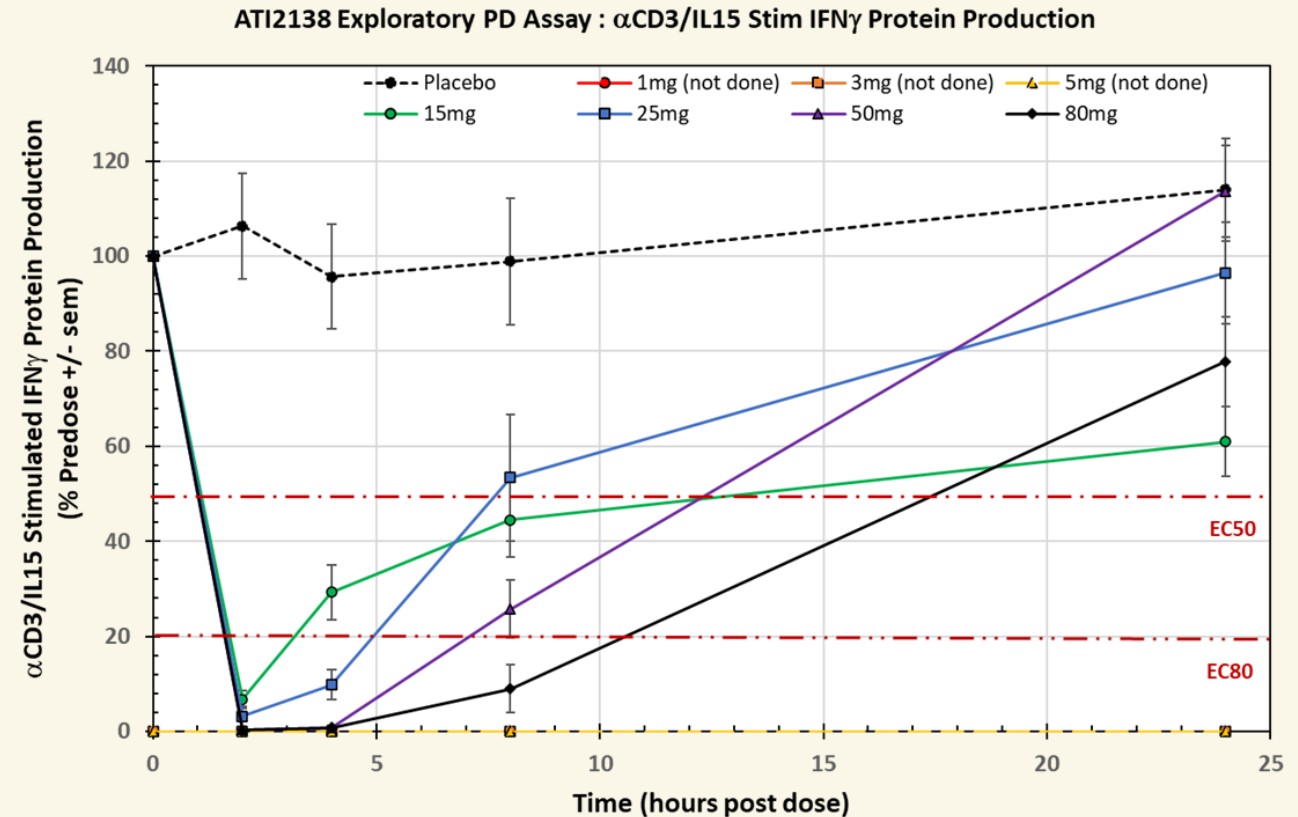
1. Data on file; 2. Graham RM. Cleve Clin J Med. 1994;61(4):308-313; 3. Siliciano JD, et al. Proc Natl Acad Sci U S A. 1992;89(23):11194–11198; 4. Robinson MF, et al. [published online ahead of print, 2020 May 18]. Arthritis Rheumatol. 2020; 5. Russell SM, et al. Science. 1995;270(5237):797-800

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 α CD3/IL-15-induced IFN γ protein production

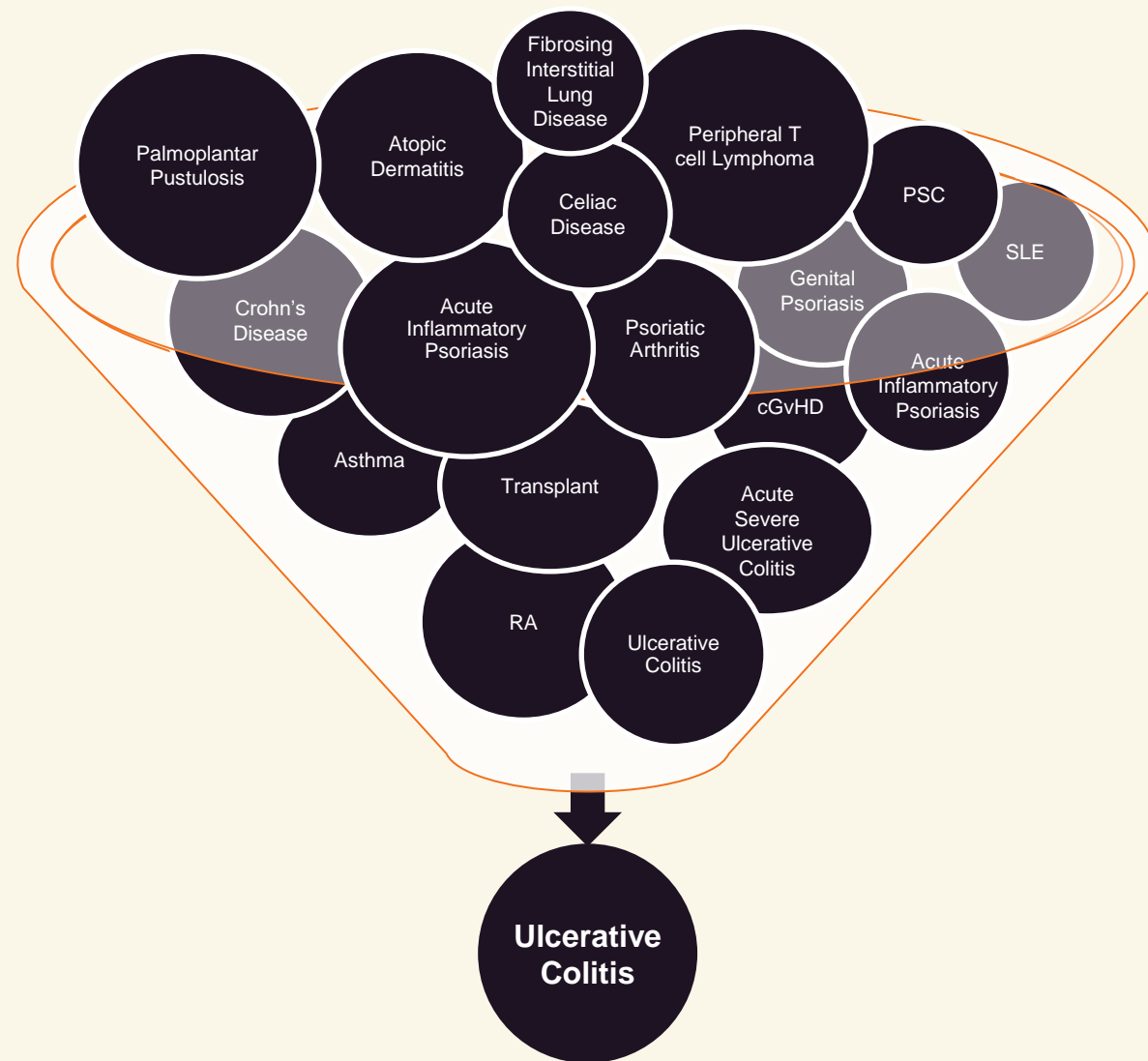


Pharmacodynamic Dual Stimulation Assay

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 disease¹
- Elevated expression of ITK in colonic mucosa of UC patients¹
- Similar T cell signaling of pathway of cyclosporine, 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 future²



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 Q4 2022 with \$230M 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



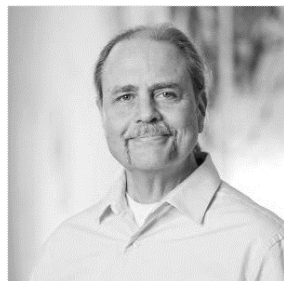
Douglas Manion
Chief Executive
Officer

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

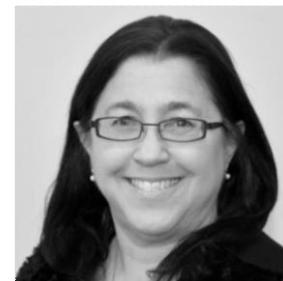
> 100 publications and
patents (>30 total on
kinases)



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
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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.

2023 Expected Data Readouts

