EMPOWERING PATIENTS THROUGH
KINOME INNOVATION

Company Overview

February 2020

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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 for initiation and completion of clinical trials, the availability of data from these trials and the timing of its regulatory submissions related to these trials. 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, 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, 2019, 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" section of the Investors page 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. This data involves 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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Strategy: *Development stage biotechnology company focused on immuno-inflammatory diseases*

LEADERSHIP

- Physician/Scientist founded and led
- Kinome experts - combined 300+ years of R&D experience immunology and inflammation
- World class ex-Pfizer kinase and ex-GSK immunology R&D leadership

KINect™ PLATFORM
Proprietary Discovery Engine

- Versatile platform with multiple approaches for difficult to drug kinases in precedented pathways
- Fully integrated discovery and development team
- Dedicated to the design of innovative, kinase targeted medicines for immuno-inflammatory diseases
- Positioning small molecule drug candidates to parallel or exceed efficacy of high value biologics

INNOVATIVE PIPELINE
(investigational drug candidates)

ATI-450 – MK2i
- Oral anti-TNF, anti-IL1, anti-IL6
- Novel target for the potential treatment of various immuno-inflammatory indications

ATI-1777-Topical Soft-JAK1/3i
- Innovative treatment limiting systemic exposure for the potential treatment of moderate-to-severe atopic dermatitis (AD)

ATI-2138 - ITK/TXK/JAK3i
- Dual inhibitor of T-cell and cytokine receptor for the potential treatment of immuno-inflammatory diseases

R&D Leadership Team

Experienced team with deep scientific and operational experience

David Gordon
Chief Medical Officer

Former SVP, R&D at GSK. Led discovery and development teams in Immuno-Inflammation and Dermatology leading to multiple successful NDAs, including NUCALA® & BENLYSTA®

Joseph Monahan, PhD
Exec. VP R&D
(Head of Discovery)

Former Executive Director, Pfizer Inflammation Research and Leader of Global Kinase Technology Team

>95 publications and patents (>30 total on kinases)

Walter Smith
SVP, R&D

Former VP Research & Global Head, Pfizer Inflammation, co-leader of Pfizer Licensing Team

Delivered 8 clinical candidates, 6 INDs and 1 NDA in inflammation and cancer

Jon Jacobsen, PhD
VP, Chemistry

Former Research Fellow and Director, Pfizer Chemistry

>100 publications and patents (15 total on kinases)

Project Lead for PFE JAK Program

Paul Changelian, PhD
VP, Biology

Immunologist/drug discovery leader at pharma (Pfizer & biotech)

Validated JAK 1/3 as target for transplant/RA/psoriasis, leading to approval of XELJANZ®

David R Anderson, PhD
Sr. Director, Discovery, Early Development

Former research project leader at Pfizer. Director of Chemistry at Mnemosyne, Luc, Cadent.

Inventor of 6 clinical candidates and author of 40 peer reviewed publications and patents

Gary DeCrescenzo
SVP, Pharm R&D

Former Exec. Director, Pfizer. Site Head for Medicinal & Structural Chemistry. >100 patents. Co-inventor of multiple drug candidates

Pipeline

Program	Indication(s)	Preclinical	Phase 1	Phase 2	Phase 3
ATI-450 MK2 Inhibitor *Oral*	Rheumatoid Arthritis + Additional Immuno-inflammatory Indication				
ATI-1777 JAK1/JAK3 Inhibitor *Soft Topical*	Atopic Dermatitis (moderate-to-severe)				
ATI-2138 ITK/TXK/JAK3 Inhibitor *Oral*	Psoriasis, Inflammatory Bowel Disease				
JAK1/JAK3 Inhibitor *Oral, gut-restricted*	Inflammatory Bowel Disease				
ITK/TXK/JAK3 Inhibitor *Oral, gut-restricted*	Inflammatory Bowel Disease				

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The Kinase Opportunity and Challenge

Creating New Medicines Targeting Previously Inaccessible Kinome Targets

Medically Important and Productive Target Class

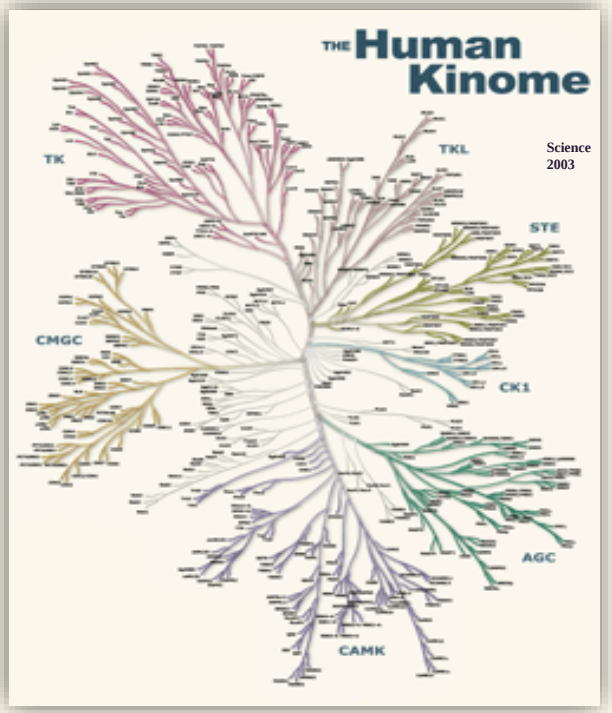
OFEV (nintedanib) capsules 150mg
Bosulif bosutinib
IBRANCE palbociclib
IRESSA
Inlyta axitinib
imbruvica (ibrutinib) 140mg capsules
ZELBORAF (vemurafenib) tablets
ICLUSIG (ponatinib) tablets 45 mg, 15 mg
COMETRIQ (cabozantinib)
gleevec (imatinib mesylate) tablets
GILOTRIF (afatinib) tablets
Tarceva erlotinib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

~36 Marketed Drugs

~$48B*

Annual Sales of Kinase Drugs

Most Members of the Kinome Remain Unexplored



518 Members

>90% of the Human Kinome remains undrugged

These drugs target less then 5% of the kinome

* Bologa C, et al. Unexplored opportunities in the druggable human genome. *Nat Rev Drug Discov*. 2018.
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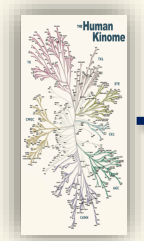
KINect Platform
Developing Kinase Drug Candidates Rapidly & Efficiently

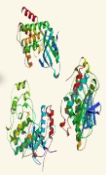
TARGET SELECTION & VALIDATION → **KINect Platform – LEAD GENERATION** → **ASSET GENERATION**

500+ Kinases



>300 Cysteine Kinases

Select Cysteine Kinases



w/Published Crystal Structures

Assess Target Confidence

- Disease
- Genetics
- Safety
- Distribution

Custom Kinase and Immune Assays

Proprietary Chemical Library

ANALYSIS → MODELING → DESIGN → SYNTHESIS

Schrödinger™ Enabled Drug Design

Proprietary Portfolio
- MK2 Inhibitor
- JAK Inhibitors
- ITK Inhibitors

Strategic Partner(s)
- Project 1
- Project 2
- Project 3

- **Proprietary Library:** **High affinity/selective drug scaffolds**
- **Faster Path:** **Decrease time to Lead Optimization by half or more**
- **Multiple Approaches:** **Design approach specific to each kinase**

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KINect™ Platform Demonstrated Success
Reversible and Covalent

MK2 Inhibitor	Tissue Restricted JAK and ITK Inhibitors	Covalent ITK Inhibitors
• Oral anti-TNF, anti-IL1, and anti-IL6 MK2 kinase inhibitor drug • Novel approach for a difficult to target kinase • ATI-450 (investigational compound) Phase 1 clinical trial preliminary data available	• Potential approaches to achieve efficacy with improved safety • ATI-1777 (investigational compound): Soft, topical drug for the potential treatment of moderate-to-severe AD • Gut-restricted inhibitor for the potential treatment for inflammatory bowel disease	• ITK T cell kinase inhibitors for autoimmune diseases • Reversible inhibition largely unsuccessful • Oral and topical covalent drug candidates developed • Oral: ATI-2138 (investigational compound) IND enabling work
Unique Substrate Selective Drug Design	**Tailoring physico-chemical and potency properties**	**Covalent Inhibition: for difficult to target kinase**

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Market Overview of Select Inflammatory Indications

	RA (moderate - severe)	Psoriasis (moderate - severe)	Ulcerative Colitis (moderate - severe)	Crohn's Disease (moderate - severe)	Atopic Dermatitis (moderate - severe)
2018E WW Sales[1]	~$25B	~$15B	~$5B	~$11B	~$1B
Estimated Peak Market (WW)[2]	~$25-30B	~$20-25B	~$8-12B	~$15B	~$8-12B
Prevalent US Moderate/Severe Population[3]	~1,000K+	~1,000-1,300K	~400-500K	~350-450K	~300-700K
Approved Agents (per target)	TNF-α: 5 CD20: 1 JAK: 2 Integrin α4β7: 1 Other: 3	TNF-α: 3 IL-12 / IL-23: 2 IL-17A: 2 PDE4: 1	TNF-α: 2 Integrin α4β7: 1 JAK: 1	TNF-α: 3 IL-12 / IL-23: 1 Integrin α4β7: 1	IL-4R: 1
Agents in Clinic (per target)	BTK: 9 JAK/STAT: 5 IL-6: 3 TNF-α: 1 T-cell Receptor: 1 Others: 41	IL-23: 2 IL-17 / IL17R: 4 JAK/STAT: 2 Others: 7	JAK/STAT: 4 IL-23: 4 S1P-R: 2 Integrins: 2 Others: 12	JAK/STAT: 5 IL-23: 5 S1P Receptor: 3 Integrin α4β7: 1 Others: 12	JAK/STAT: 4 IL-33: 2 IL-13: 2 IL-31: 2 OX40: 2 Others: 8
Opportunity for New Treatments	Orals, Improved risk/benefit, novel mechanism	Oral, novel mechanism, improved safety	Gut-restricted (improved safety)	Gut-restricted (Improved safety)	Improved risk/benefit, topical in moderate to severe

* Auster M, et al. Something Big Is Getting Bigger [research note]. New York, NY: Credit Suisse Equity Research; 2019.
[1] Estimates of total sales per indication from EvaluatePharma.
[2] CS projections: based on US branded pricing.
[3] Assumed peak treatable population with biologics/novel agents in the US: RA 350-400k / Psoriasis 300-350k / Ulcerative Colitis 225-275k / Crohn's 225-275k / Atopic Dermatitis 150-200k.

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ATI-450: MK2 Inhibitor

(Investigational Drug Candidate)

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MK2 Inhibitor – Potential Alternative to Injectable, Anti-Cytokine Biologics and JAK Inhibitors for Immuno-Inflammatory Diseases

- MK2* is an attractive drug target because it drives pro-inflammatory cytokine expression
- The effects of inhibiting MK2 mirror the effects of anti-inflammatory biologics[1]
  - ✓ **anti-TNF**: HUMIRA® (adalimumab), ENBREL® (etanercept), REMICADE® (infliximab)
  - ✓ **anti-IL1**: KINERET® (anakinra), ILARIS® (canakinumab), ARCALYST® (rilonacept)
  - ✓ **anti-IL6**: KEVZARA® (sarilumab), ACTEMRA® (tocilizumab)
- Oral: Small molecule MK2 inhibitor
  - ✓ ATI-450, an oral small molecule that inhibits MK2 via a novel MOA which involves binding to a drug "pocket" created in the p38α/MK2 complex[2]
  - ✓ ATI-450 has shown marked inhibition of TNFα, IL1β, IL8 and IL6 in *ex vivo* stimulated blood samples collected from healthy volunteers in Phase 1[1]

* MK2 = Mitogen-activated protein kinase-activated protein kinase 2

1 Data on file.

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

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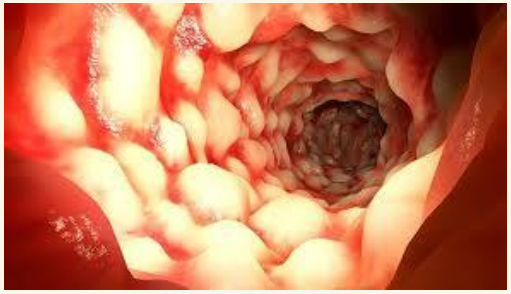
MK2-driven Cytokines are Central to Many Diseases

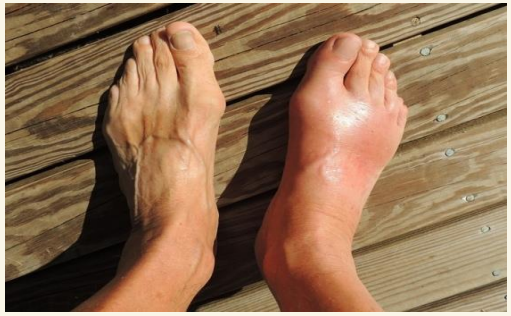
Inflammatory bowel disease



Rheumatoid arthritis /
Juvenile idiopathic arthritis

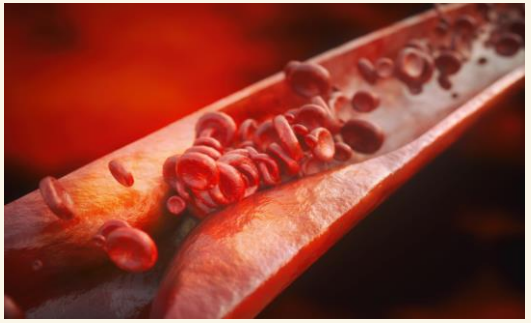
Cancer

Gout

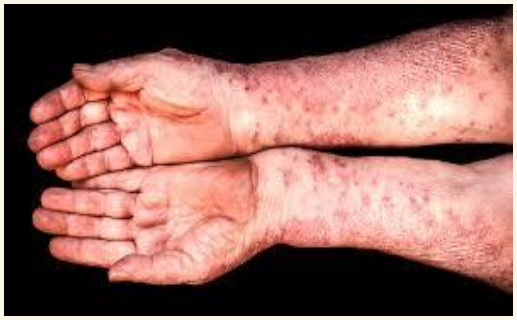


**TNFα,
IL1β, IL6**

Cardiovascular /
cerebrovascular disease

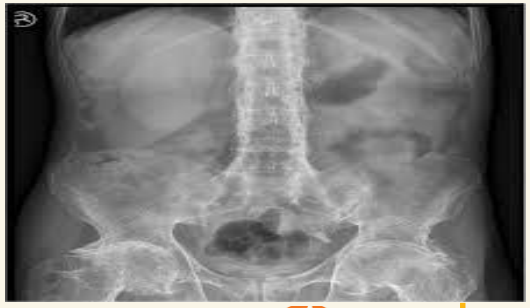


Psoriasis / psoriatic arthritis



Asthma / COPD

Ankylosing spondylitis



Singh RK, et al. *Pharmacol Reports*. 2017;69:746-756.

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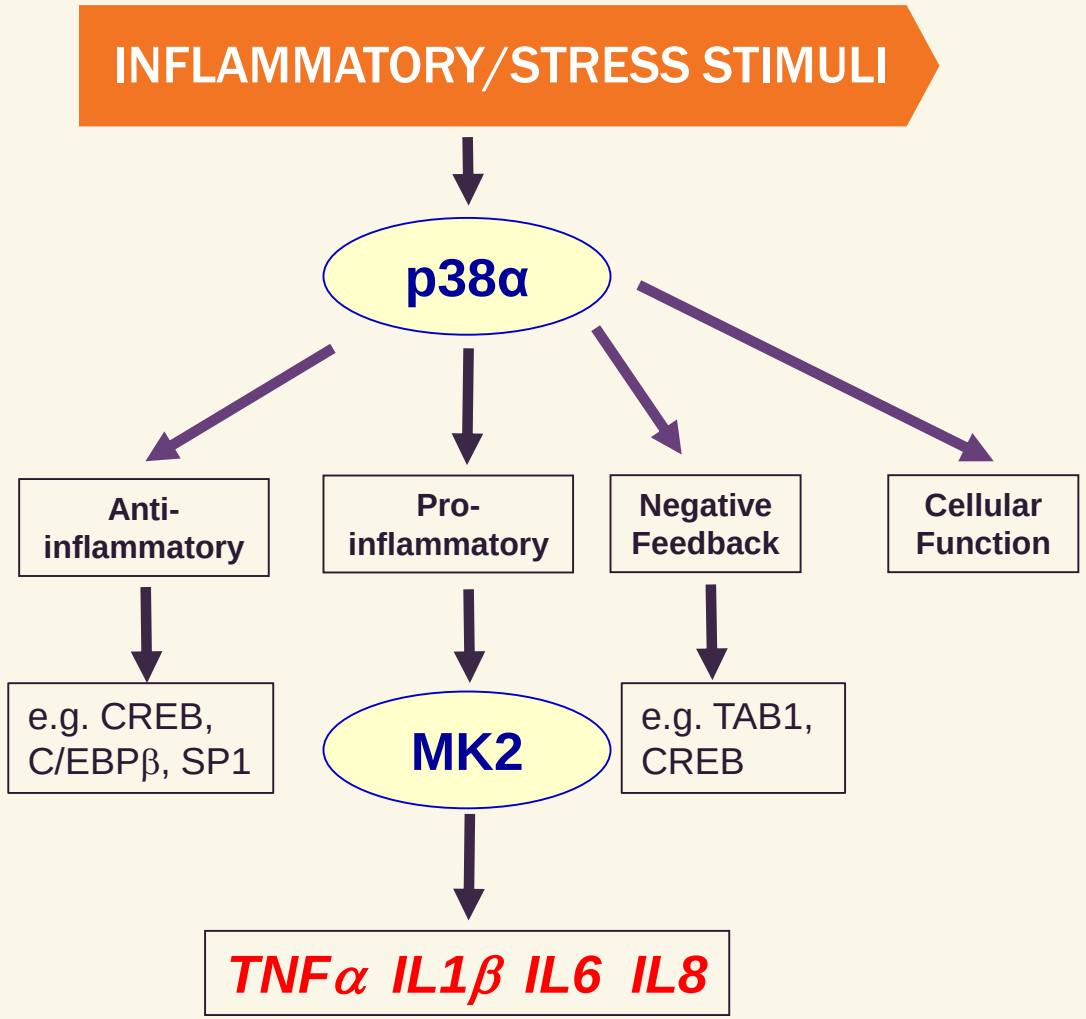
Evolution in Understanding of a Well-Known Path

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 in RA and IBD
- p38α phosphorylates over 60 substrates - yet MK2 drives the proinflammatory node of this pathway
- MK2 has been a high priority therapeutic target since 1999 but has proven very difficult to drug
- ATI-450 locks MK2 in a catalytically inactive state – a unique MOA – which may be a viable approach to target MK2



* 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.

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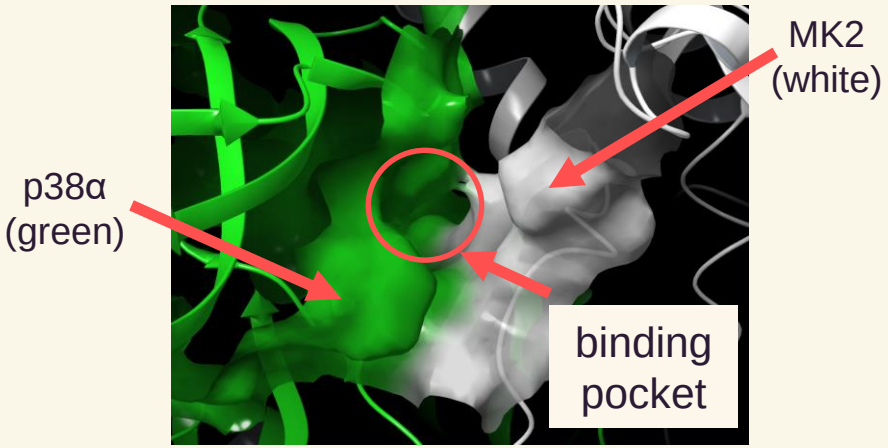
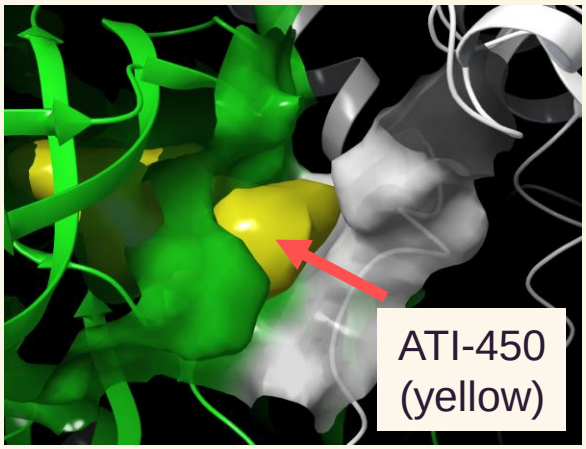
Capturing MK2 in an Inactive State



Crystal structure of the p38α/MK2 complex



ATI-450 (yellow) docked in the pocket

- In the nucleus, inactive MK2 and p38α dock in a high affinity complex that exhibits a binding pocket formed by juxtaposed walls of both proteins
- ATI-450 binds to both walls of the pocket, stabilizing the complex and preventing MK2 activation

ATI-450 locks MK2 in a catalytically inactive state – a unique MOA

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

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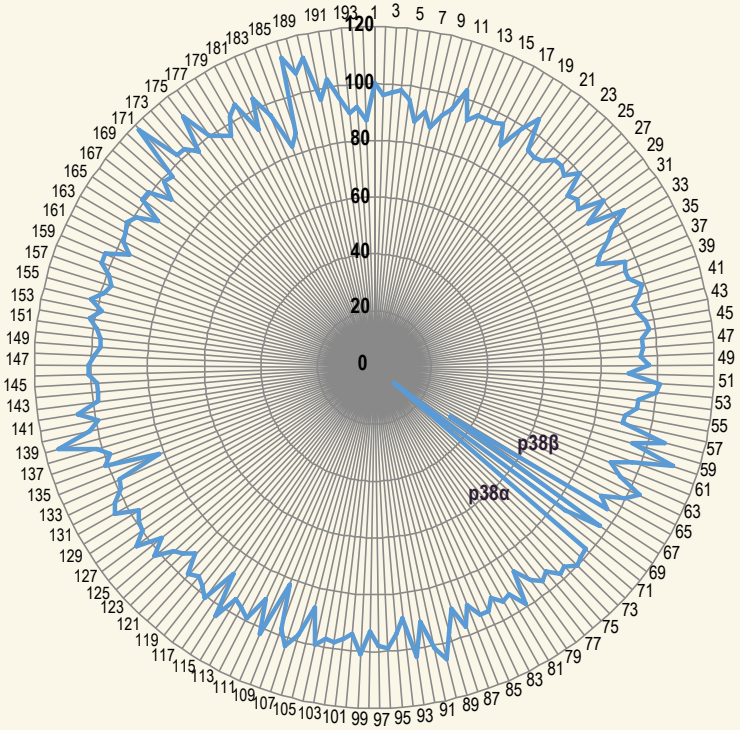
ATI-450 selectivity

Human Kinome Selectivity[1]



- ATI-450 (5μM) was tested vs 193 kinases
- >350-fold binding selectivity on all kinases in this panel except p38α and p38β

MK2 Pathway Selectivity

ATI-450 is highly selective for the p38/MK2 complex vs. other p38 substrates[1]

Assay	Fold Selective
p38α/MK2	1
p38α/ATF2	700
p38α/PRAK	750

ATI-450 binds to the p38α/MK2 complex with higher affinity than either p38 or MK2 alone**

Assay	Fold Selective
p38α/MK2	1
p38α/p38tide*	51
MK2/HSP27	>550

* Optimized p38 peptide substrate
** Data on file.
1 Wang C, et al. *J Exp Med*. 2018;215(5):1315-1325.

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Animal Models Supporting the Development of ATI-450 in Immuno-Inflammatory Diseases

Therapeutic Area	Animal Model	Reference
Rheumatoid Arthritis / Psoriatic Arthritis	Rat streptococcal cell wall arthritis model • Protection against bone deterioration • Protection against lethality Inhibition of cellular IL1β mRNA stability & translation	Wang C, et al. *J Exp Med.* 2018;215(5):1315-1325.
Inflammatory Bowel Disease	Adoptive transfer mouse model of colitis • Endoscopy scores show disease control • Decreased inflammatory infiltrate • Protected structural integrity of mucosa	Strasser S, et al. *Integrative Biology*. 2019;11(7):301-314.
Cryopyrin-Associated Periodic Syndromes (CAPS)	Murine NOMID (severe form of CAPS) transgenic model Human CAPS PBMC* IL1β modulation	Wang C, et al. *J Exp Med.* 2018;215(5):1315-1325.

* PBMC = Peripheral blood mononuclear cells

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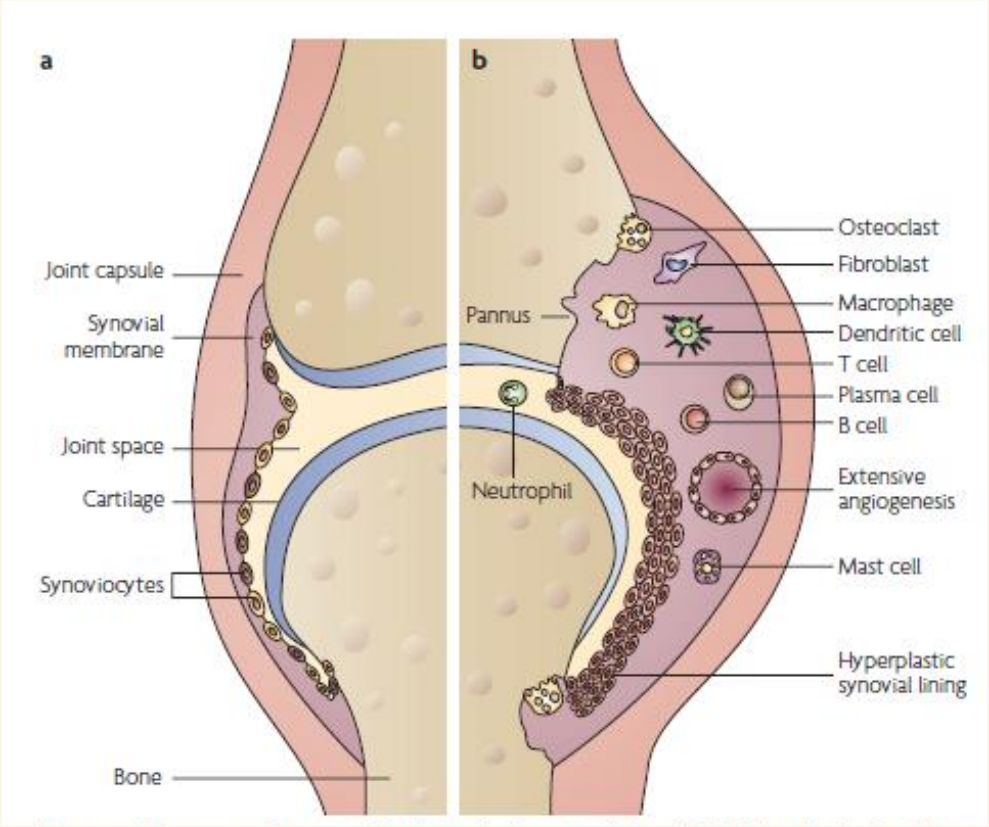
MK2 – Potential Effect in Rheumatoid Arthritis

ATI-450 regulates cells and cytokines involved in RA

MK2 is a key regulator of pathogenic signals in chronic immuno-inflammatory diseases

Normal Joint

RA Joint



Strand V, et al. *Nat Rev Drug Discov.* 2007;6(Jan 2007):75-92.

Cells

Monocyte/Macrophage

Osteoclast

Epithelial Cells

RA Synovial Fibroblast

Chondrocytes

Cytokines

TNFα, IL1β, IL1α

IL6, IL8, IL18, RANKL

ATI-450: for bold items above data on file and Wang C, et al. *J Exp Med*. 2018;215 (5):1315-1325.

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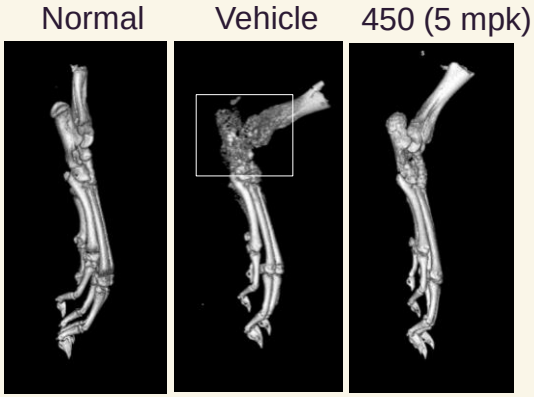
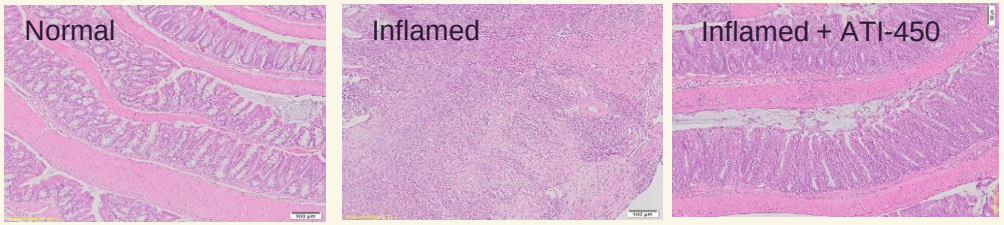
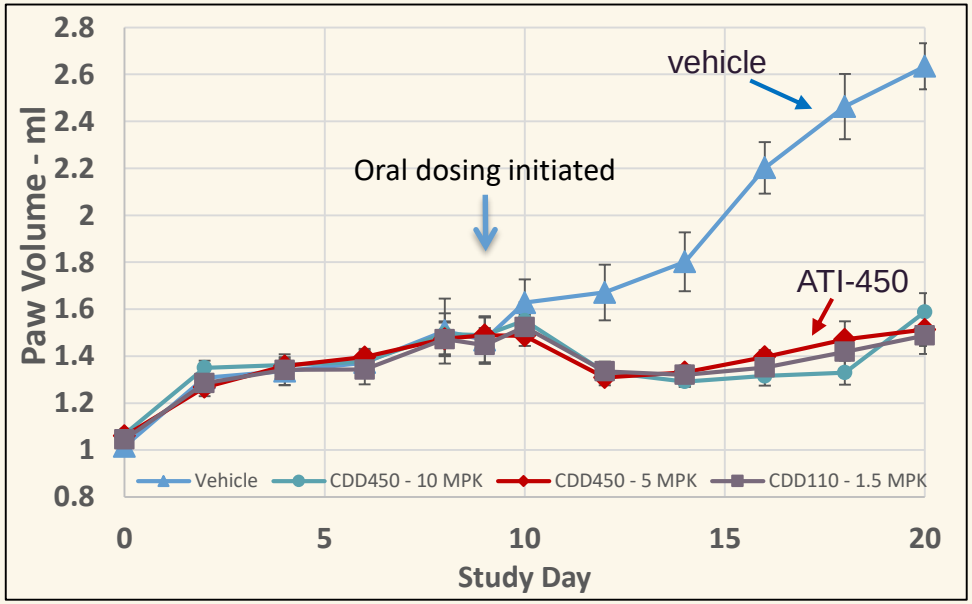
In vivo Preclinical Data of MK2 Pathway Inhibitor ATI-450

Joint Protection in Rat Arthritis Model[1]

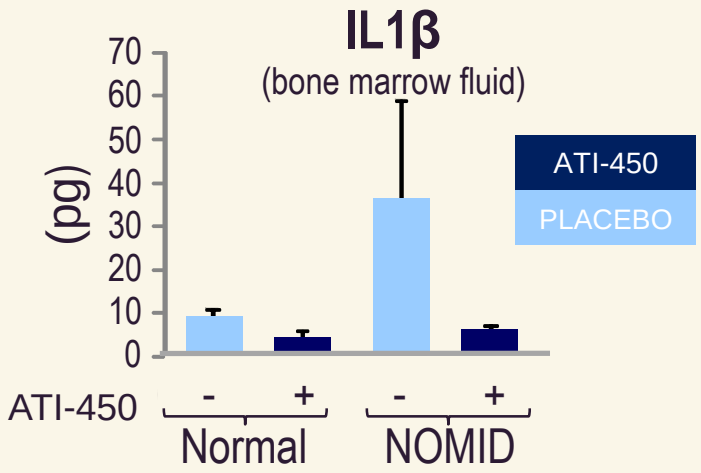


Blockade of Gut Inflammatory Infiltrate in Murine Adoptive Transfer Ulcerative Colitis Model[2]





Cytokine Modulation in Orphan Autoinflammatory Disease (CAPS)[1]



1 Wang C, et al. *J Exp Med*. 2018;215(5):1315-1325.
2 Strasser S, et al. *Integrative Biology*. 2019;11(7):301-314.

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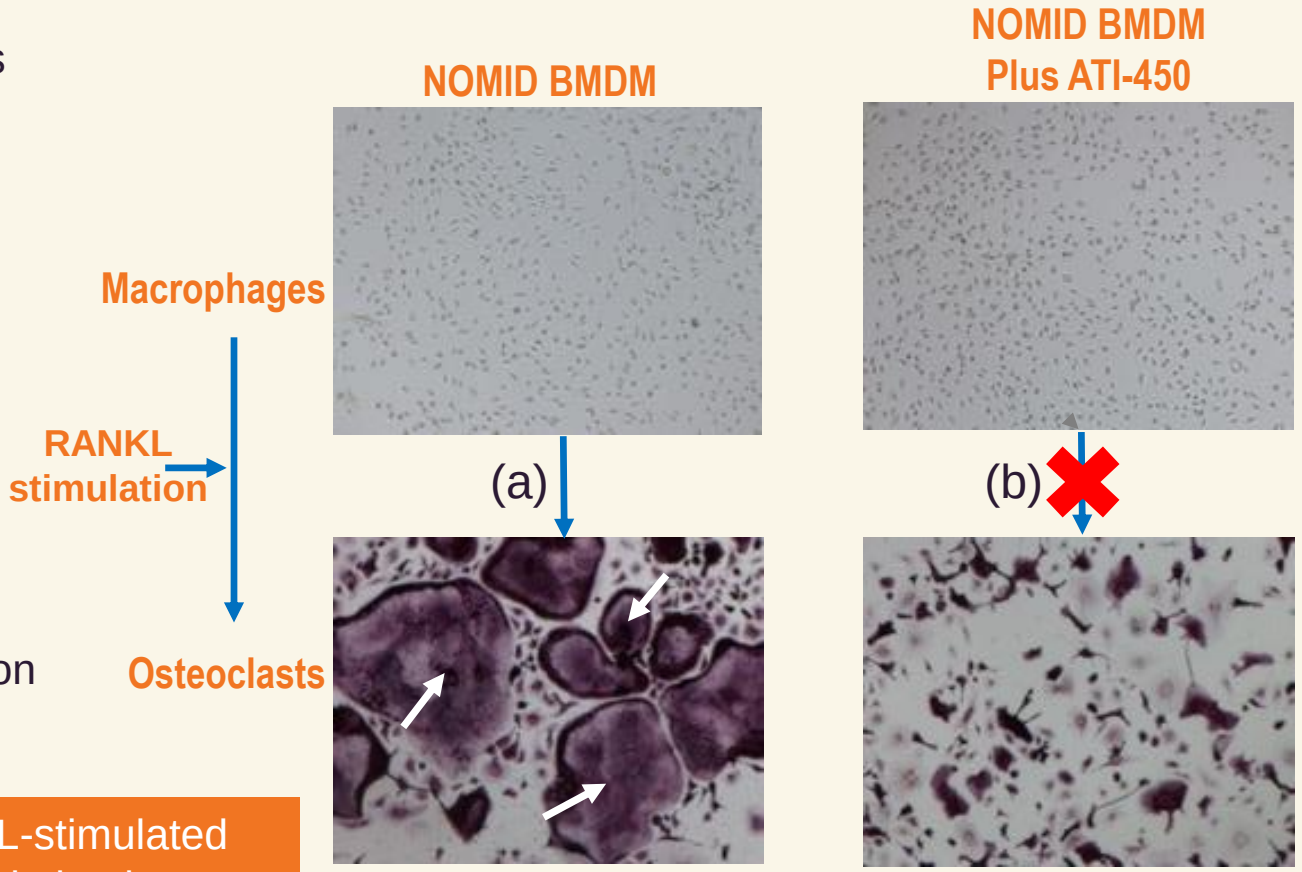
Mouse Model: ATI-450 Inhibits RANKL-induced Osteoclastogenesis

Bone marrow derived macrophages (BMDM) from NOMID mice

- In CAPS, osteoclastogenesis gives rise to low bone mass (osteopenia)
- (a) When bone marrow derived macrophages (BMDM) from NOMID mice are stimulated with RANKL (RANK ligand), they differentiate into osteoclasts
- (b) ATI-450 blocks this macrophage differentiation

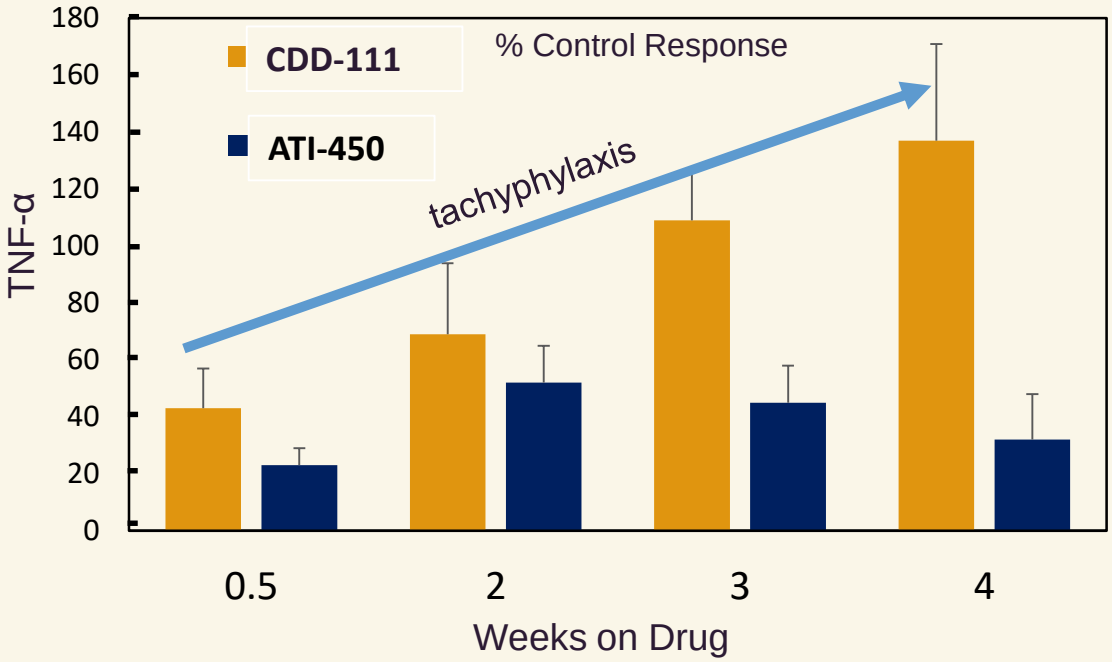


ATI-450 inhibits RANKL-stimulated macrophage differentiation into osteoclasts from NOMID mice

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

Mouse Model: LPS-Induced TNFα Production
ATI-450 demonstrated durable response (no tachyphylaxis)

- Global investigational p38 inhibitor CDD-111 lost inhibition over time
- **MK2 inhibitor ATI-450 (investigational compound) demonstrated durable response (no tachyphylaxis)**



- CDD-111 and ATI-450 administered to mice in feed starting day 1 and continuing through day 28
- At the time point indicated, mice were LPS challenged and blood TNFα levels determined

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

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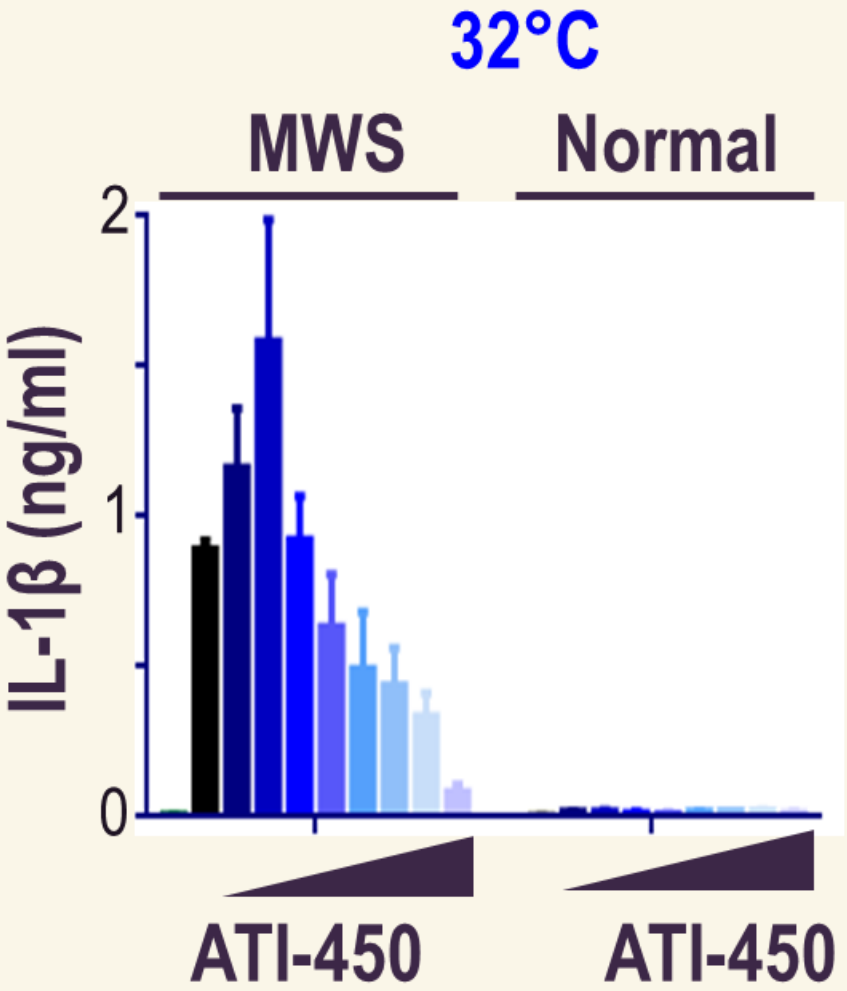
Ex vivo Preclinical Data: ATI-450 Inhibits IL1β Expression in PBMCs from a Patient with CAPS



- Peripheral blood mononuclear cells (PBMCs) were isolated from patients with CAPS and healthy controls.
- In patients with CAPS (Muckle Wells Syndrome; MWS), IL1β expression is triggered by exposure to low temperatures.
- PBMCs from patients with CAPS spontaneously produced high amounts of IL1β at 32°C but not at 37°C.
- ATI-450 blocks temperature stress induced IL1β production.

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

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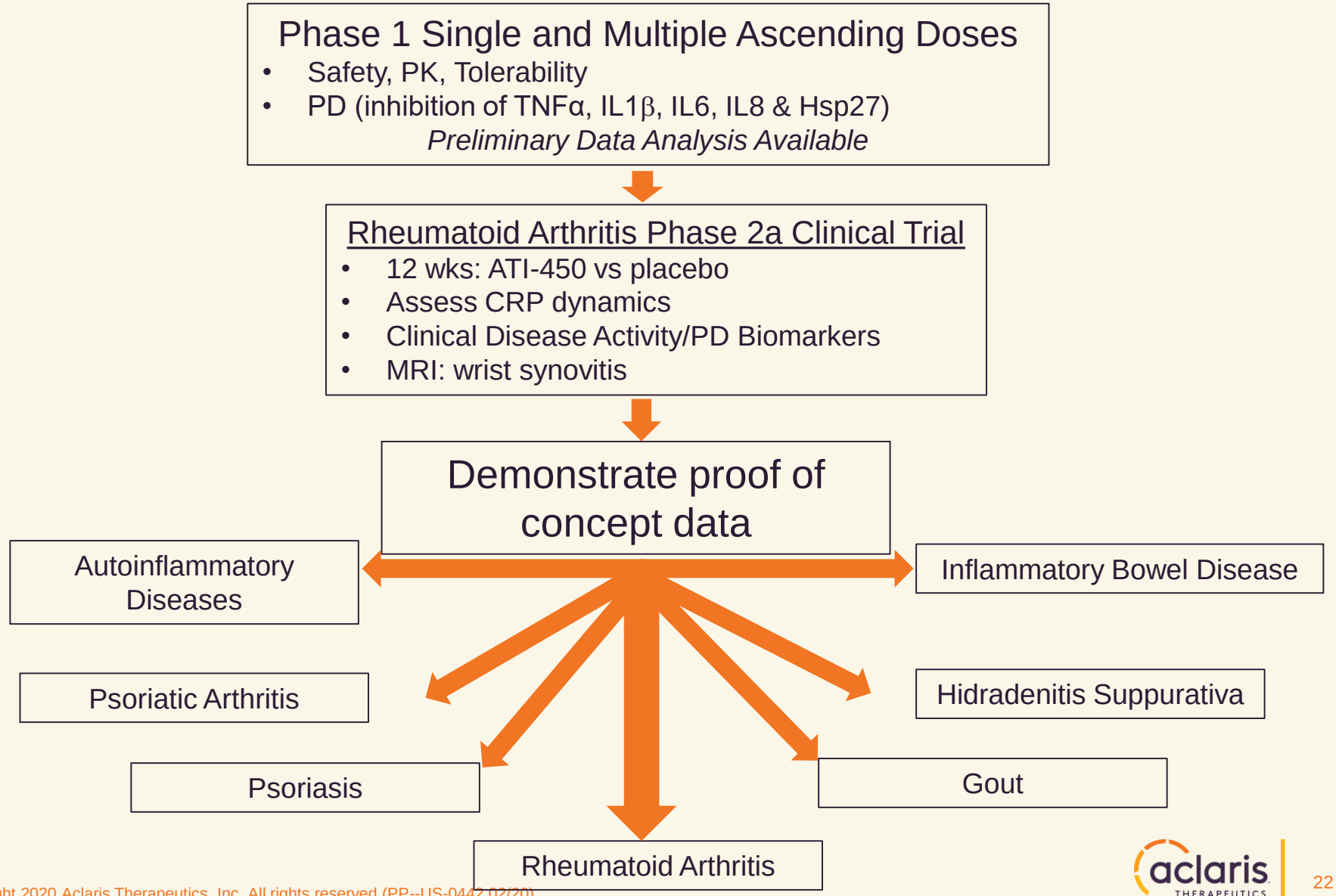
ATI-450 Clinical Development



ATI-450-PKPD-101 SAD/MAD Phase 1 Trial

- First-in-human, randomized, observer-blind, placebo-controlled trial
  - ✓Single Ascending Doses and Multiple Ascending Doses (SAD/MAD)
- Objectives:
  - ✓Primary
    - To assess the safety, tolerability, and pharmacokinetics (PK) profile of ATI-450, an investigational oral MK2* inhibitor compound
  - ✓Secondary
    - To assess the effect of food on the PK of ATI-450
    - To explore the pharmacodynamics (PD) of ATI-450
    - To evaluate the potential for an interaction with methotrexate

* MK2 = Mitogen-activated protein kinase-activated protein kinase 2

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ATI-450-PKPD-101
Trial Design and Demographics

- Three-Part Study:
  - ✓ Part A: single ascending dose (SAD) plus food effect (n=32)
    - 4 cohorts: 10mg, 30mg, 50mg, 100mg (100mg repeated with high fat meal)
    - 8 subjects (6 active, 2 placebo). Single dose after overnight fast
  - ✓ Part B: multiple ascending dose (MAD) (n=30)
    - 3 cohorts: 10mg, 30mg, 50mg all BID for 7 days
    - 10 subjects (8 active, 2 placebo)
  - ✓ Part C: methotrexate (MTX) drug-drug interaction (DDI) (n=15)
    - 1 cohort: MTX day 1 and 8. ATI-450 on days 2-9
    - 15 subjects all dosed with active
- Demographics: (All dose groups, all parts)
  - ✓ Age: Mean 34 years
  - ✓ Gender: 44 female/33 male
  - ✓ Race: White-40, Black-32, Other-5

ATI-450-PKPD-101

Safety: ATI-450 Generally Well-Tolerated

Most Common Adverse Events (≥2 subjects in the trial)

SAD/MAD cohorts (blinded)

Preferred Term	ATI-450 n (%) (n=48)	Placebo n (%) (n=14)
Dizziness	6 (12.5)	0
Headache	10 (20.8)	2 (14.3)
Upper respiratory tract infection	3 (6.3)	1 (7.1)
Constipation	3 (6.3)	1 (7.1)
Nausea	2 (4.2)	1 (7.1)
Abdominal pain	2 (4.2)	0
Vomiting	0	2 (14.3)

DDI cohort (unblinded ATI-450 + MTX)

Preferred Term	ATI-450 n (%) (n=15)
Dizziness	7 (46.7)
Headache	1 (6.7)
Upper respiratory tract infection	1 (6.7)
Constipation	0
Nausea	0
Abdominal pain	0
Vomiting	0

- No serious adverse events
- No adverse events led to discontinuation of study medication
- All adverse events were mild in severity - dizziness and other adverse events caused minimal discomfort, and did not interfere with everyday activities
- A trend of a decrease in absolute neutrophil count was observed
  - ✓ No correlation with clinical sequelae
  - ✓ This effect is consistent with the pharmacodynamic profile of certain anti-TNF therapies[1]

1 Dillingh M, et al. *Front. Immunol*. 2016;7(508):1-9.
* Data on file.

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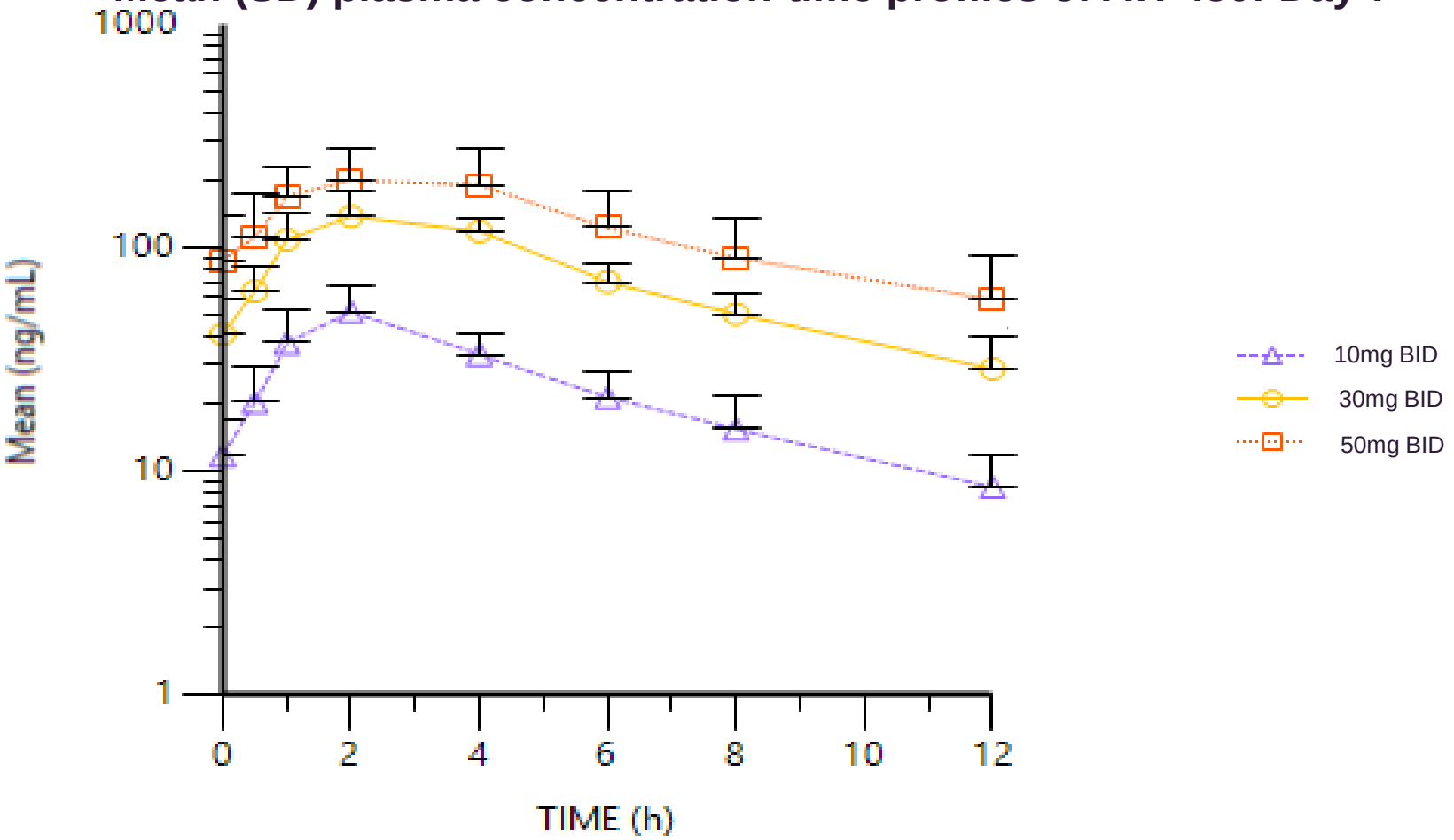
ATI-450-PKPD-101

MAD Pharmacokinetics: Dose Proportional PK

Mean (SD) plasma concentration-time profiles of ATI-450: Day 7



t½ = 9-12 hours

* Data on file

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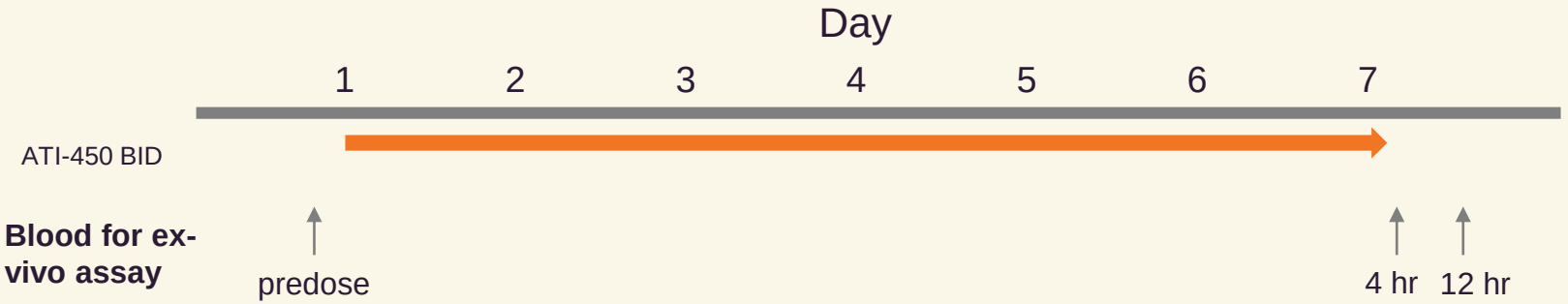
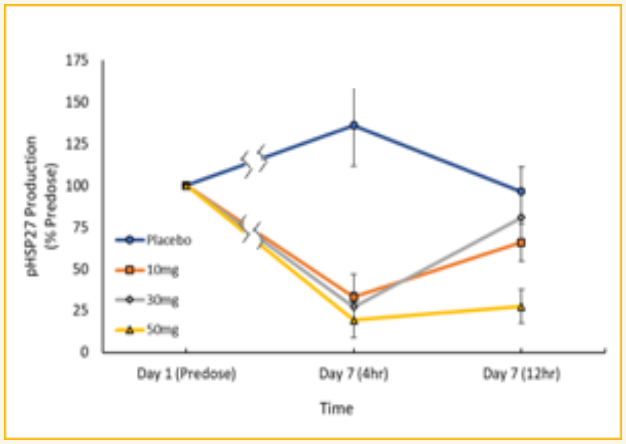
ATI-450 PD: Day 7 MAD PD Marker Time Dependence

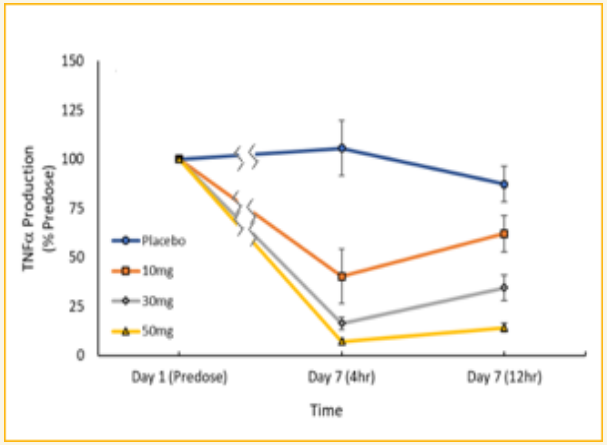
Target Biomarker pHSP27 and Cytokines TNFα and IL1β



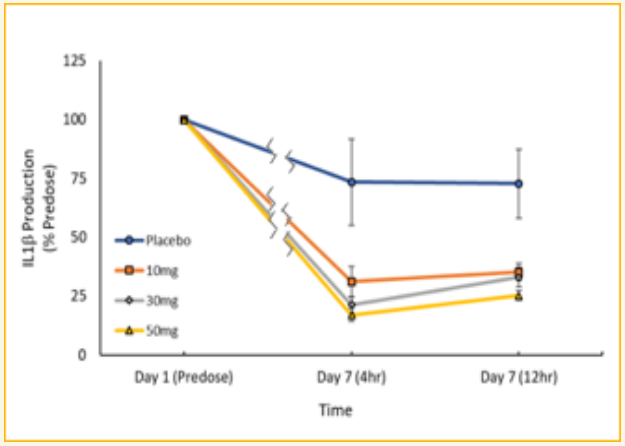
pHSP27



TNFα



IL1β



- ATI-450 dosed orally BID for 7 days in healthy subjects at doses of 10mg, 30mg and 50mg
- Day 1 (predose) is from blood taken on day 1 just prior to the first dose of ATI-450
- Samples ex vivo stimulated with LPS
- Data expressed as mean +/- SEM

* Data on file

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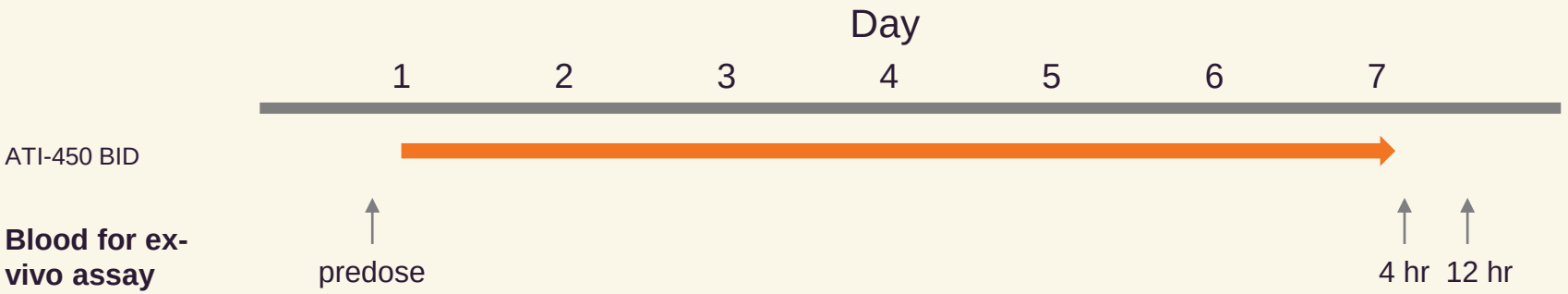
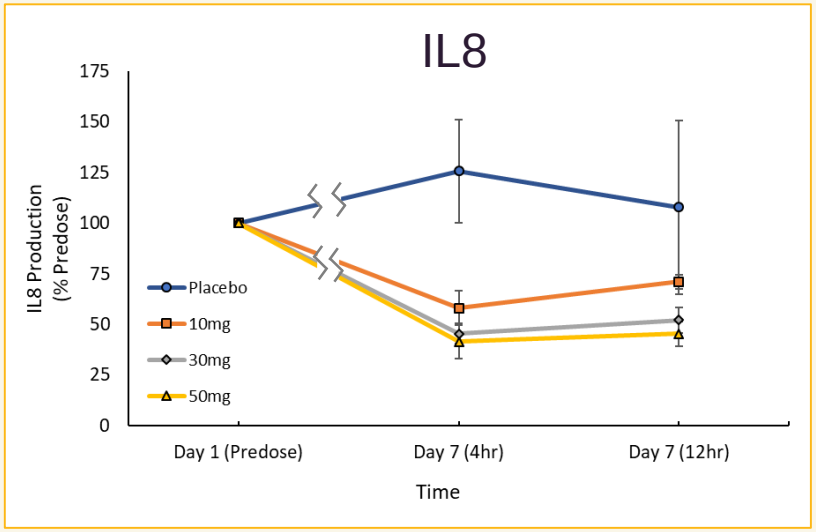
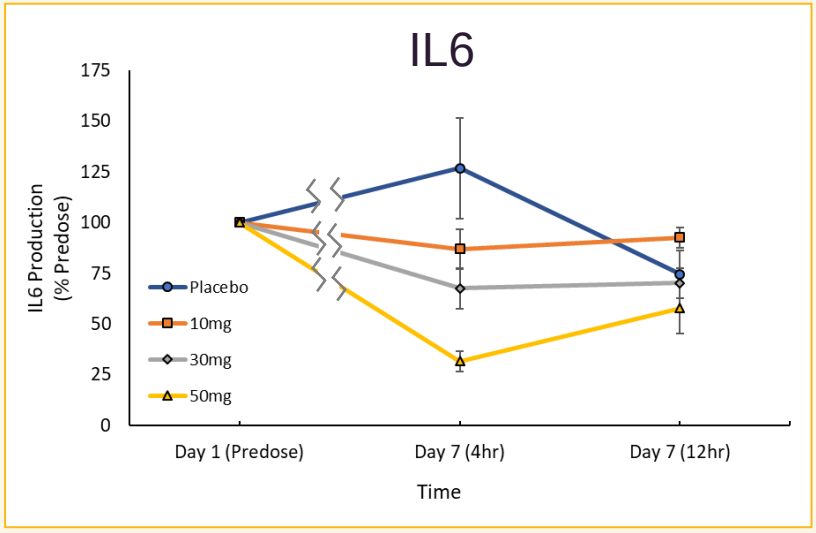
ATI-450 PD: Day 7 MAD PD Biomarker Time Dependence
Cytokines IL6 and IL8







- ATI-450 dosed orally BID for 7 days in healthy subjects at doses of 10mg, 30mg and 50mg
- Day 1 (pre-dose) is from blood taken on day 1 just prior to the first dose of ATI-450
- Samples ex vivo stimulated with LPS
- Data expressed as mean +/- SEM

* Data on file

ATI-450-PKPD-101

Plasma Levels Greater Than IC80 Throughout Dosing Interval for 4 Key PD Markers at 50mg BID Dose

ATI-450 C_{trough} and C_{max} fold above IC_{80} by dose

Analyte	Dose Level (mg BID)	Parameter	Ctrough	Cmax
IL1b	10	Fold IC80	0.3	1.5
IL6	10	Fold IC80	0.0	0.1
IL8	10	Fold IC80	0.3	1.5
pHsp27	10	Fold IC80	0.3	1.4
TNFa	10	Fold IC80	0.2	0.9
IL1b	30	Fold IC80	1.2	4.2
IL6	30	Fold IC80	0.1	0.2
IL8	30	Fold IC80	1.2	4.1
pHsp27	30	Fold IC80	1.1	4.0
TNFa	30	Fold IC80	0.7	2.4
IL1b	50	Fold IC80	2.5	6.4
IL6	50	Fold IC80	0.1	0.3
IL8	50	Fold IC80	2.5	6.2
pHsp27	50	Fold IC80	2.4	6.0
TNFa	50	Fold IC80	1.4	3.6

ATI-450 dosed at 50mg BID resulted in exposures 1.4-2.5x greater than those needed to inhibit 4 key PD markers (pHSP27, TNFα, IL1β and IL8) at an IC_{80}

* Data on file

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ATI-450: Next Steps

- Rheumatoid Arthritis Study
  - ✓ PD/safety study with early look at efficacy given small patient numbers
    - A Phase 2a, Randomized, Investigator and Patient-blind, Sponsor-unblinded, Parallel Group, Placebo-controlled Study of ATI-450 Plus Methotrexate (MTX) vs MTX Alone in Patients With Moderate to Severe Active Rheumatoid Arthritis
  - ✓ Topline data will consist of:
    - Safety and tolerability
    - Assess CRP dynamics
    - Clinical Disease Activity/PD Biomarkers
    - MRI: wrist synovitis
    - Descriptive efficacy statistics
- Additional immuno-inflammatory indication - trial being planned

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MK2 inhibitor ATI-450 Summary

- Discovered an approach to drug the target
  - ✓ Lock MK2 in a catalytically inactive state – a unique MOA
  - ✓ Multiple relevant inflammatory cytokines impacted
- Potential alternative for numerous diseases currently treated by biologics and JAK inhibitors
  - ✓ Robust efficacy in a range of inflammation and mouse cancer models[1,2]
- Phase 1 SAD/MAD Data*
  - ✓ Generally well-tolerated at all doses
  - ✓ Dose proportional pharmacokinetics and a half-life supporting BID, and potentially QD, dosing
  - ✓ Inhibits key cytokines and biomarkers in a dose-dependent way
- Proof of concept Phase 2a trial in RA expected to begin first half 2020
  - ✓ To assess safety and tolerability
  - ✓ To demonstrate clear pharmacodynamic effect and no tachyphylaxis
  - ✓ To demonstrate early signs of efficacy in a well understood disease
- Additional immuno-inflammatory indications under consideration

* Data on file

1 Murali B, et al. *Cancer Res.* 2018;78(19):1-13.
2 Wang C, et al. *J Exp Med*. 2018;215(5):1315-1325.

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ATI-1777 (Topical Soft-JAK Inhibitor)

(Investigational Drug Candidate)

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ATI-1777 (Topical Soft-JAK Inhibitor)

Novel approach for moderate to severe Atopic Dermatitis

- Atopic dermatitis (AD) is a disease of unknown origin that usually starts in early infancy and is typified by pruritus, eczematous lesions, xerosis (dry skin), and lichenification on the skin (thickening of the skin and increase in skin markings).[1]
  - ✓ Large and growing market – Projected to be $8-12 billion at peak (moderate-to-severe AD)[2]
  - ✓ Unmet need for effective and safe topical treatment for AD
  - ✓ Systemic and topical JAK inhibition has demonstrated promising results in clinical trials for treating pruritus and inflammation in AD[3]
  - ✓ In AD, a compromised skin barrier means that a topically dosed JAK inhibitor might result in pharmacologically active systemic drug levels
- Topical soft-JAK inhibitor has potential to achieve efficacy with improved safety
  - ✓ Achieve efficacy in skin while minimizing systemic JAK inhibitor toxicity
  - ✓ JAK1/3 selectivity minimizes JAK2 toxicities
- Topical formulations being optimized into a differentiated, patient-friendly emollient formulation (topical spray vs cream/ointment)
- First in human studies planned for second half 2020 in moderate-to-severe AD

1 https://emedicine.medscape.com/article/1049085-overview. Last accessed 11-1-19.
2 Auster M, et al. Something Big Is Getting Bigger [research note]. *Credit Suisse Equity Research*; 2019.
3 Shreberk-Hassidim R, et al. *J Am Acad Dermatol*. 2017;Apr;76(4):745-753.

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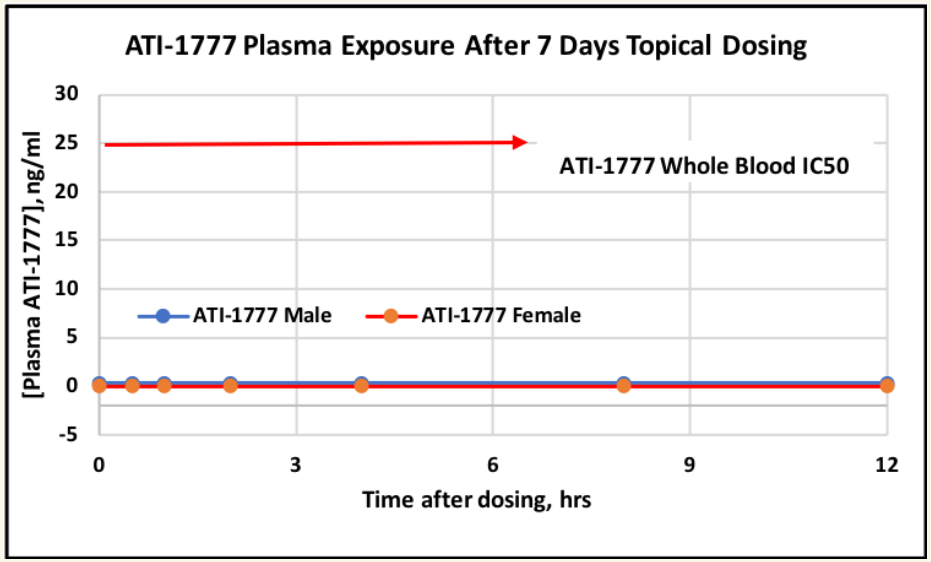
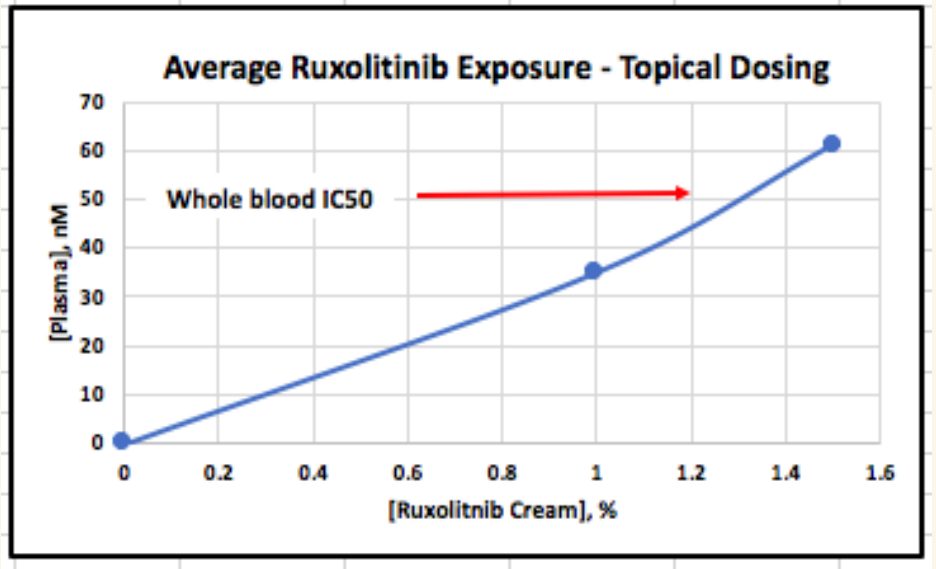
Minipig Model: ATI-1777 Nonclinical Safety Program TK Data

Tolerability/Toxicokinetic with 7-day dermal administration (non-GLP)

- No adverse effects noted (10% body surface area, QD)
- Bleeds at 0.5, 1, 2, 4, 8, 12, and 24 hours post-application: Days 1 and 6
- All plasma samples were below limit of quantification (<0.50 ng/mL) – well below cellular IC_{50}



MINIPIG[1]



HUMAN[2,3]

1 Data on file.
2 Chen X, et al. *Clin Pharmacol Drug Dev.* 2013;3(1):34–42.
3 Punwani N, et al. *Br J Dermatol.* 2015;173:989–997.

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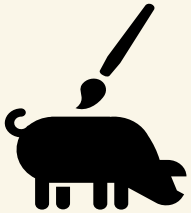
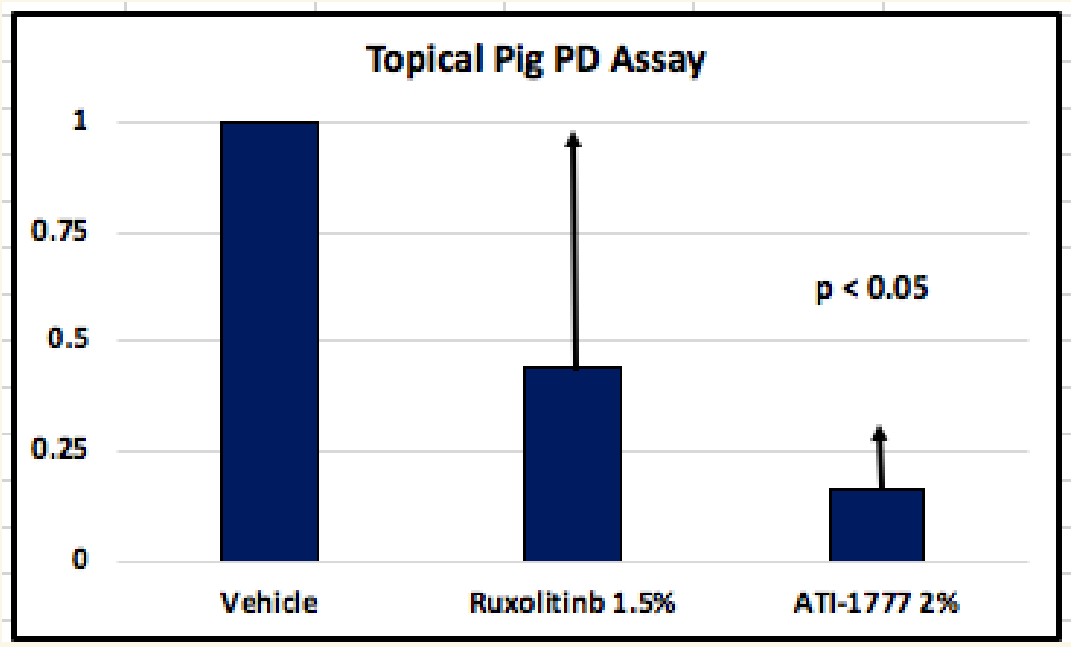
Porcine Model: ATI-1777 Blocks IL15 Induced CCL8 mRNA



Apply formulation to back of pig, wait 1 hr

Intra-dermal Injection of porcine IL15, wait 3 hr

Harvest 6 mm biopsy, prepare RNA, measure CCL8 by qPCR



- Single application of 2% ATI-1777 development formulation significantly inhibits IL15 induced gene induction (CCL8).
- Clinical topical formulation of 1.5% ruxolitinib does not significantly inhibit IL15 (CCL8) induction.

* Data on file

ATI-1777: Topical Soft-JAK Inhibitor to Target Moderate-to-Severe AD

Formulate a topical therapy for atopic dermatitis which meets the medical, aesthetic and compliance needs of patients and physicians

Approach

- Designed to be:
  - “Soft” drug to minimize the potential for systemic immunosuppression
  - JAK1/3 selective to minimize JAK2 inhibition toxicity
  - Delivered in a patient-friendly formulation to clearly differentiate it from other topical therapies

Status

- Plan to study in patients with moderate-to-severe AD
- IND-enabling preclinical safety program initiated
- Next key milestone: First In Human - 2H2020

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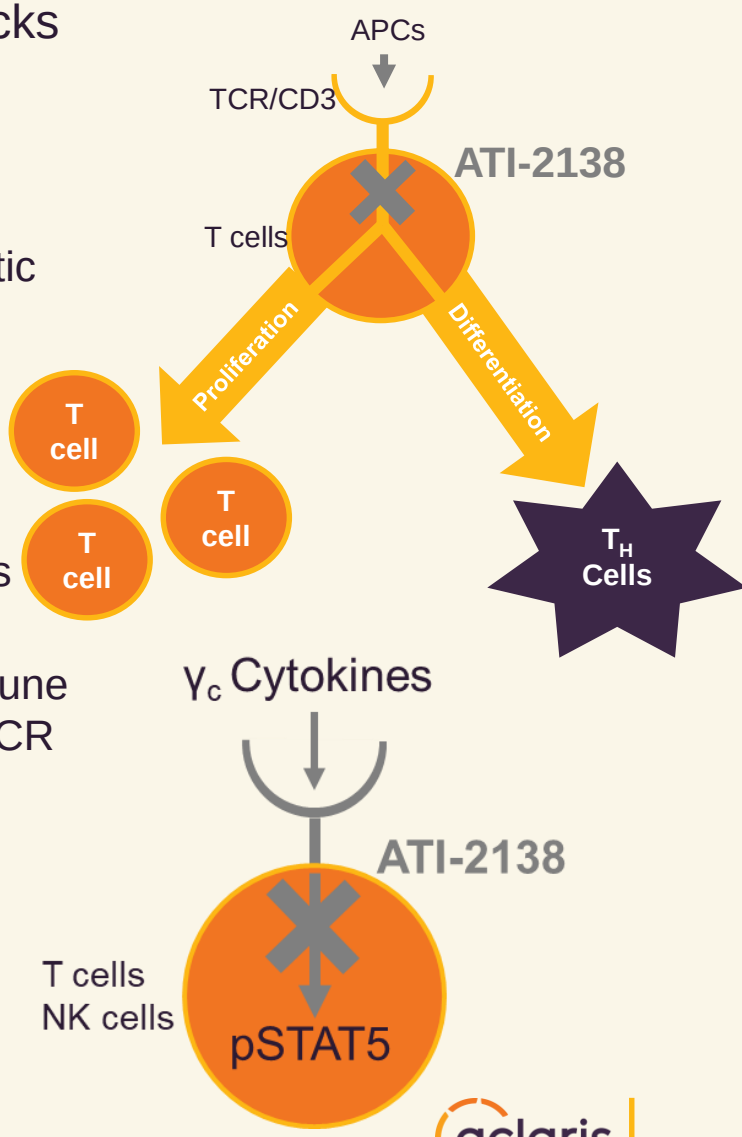
ATI-2138 (ITK/TXK/JAK3 Inhibitor)

(Investigational Drug Candidate)

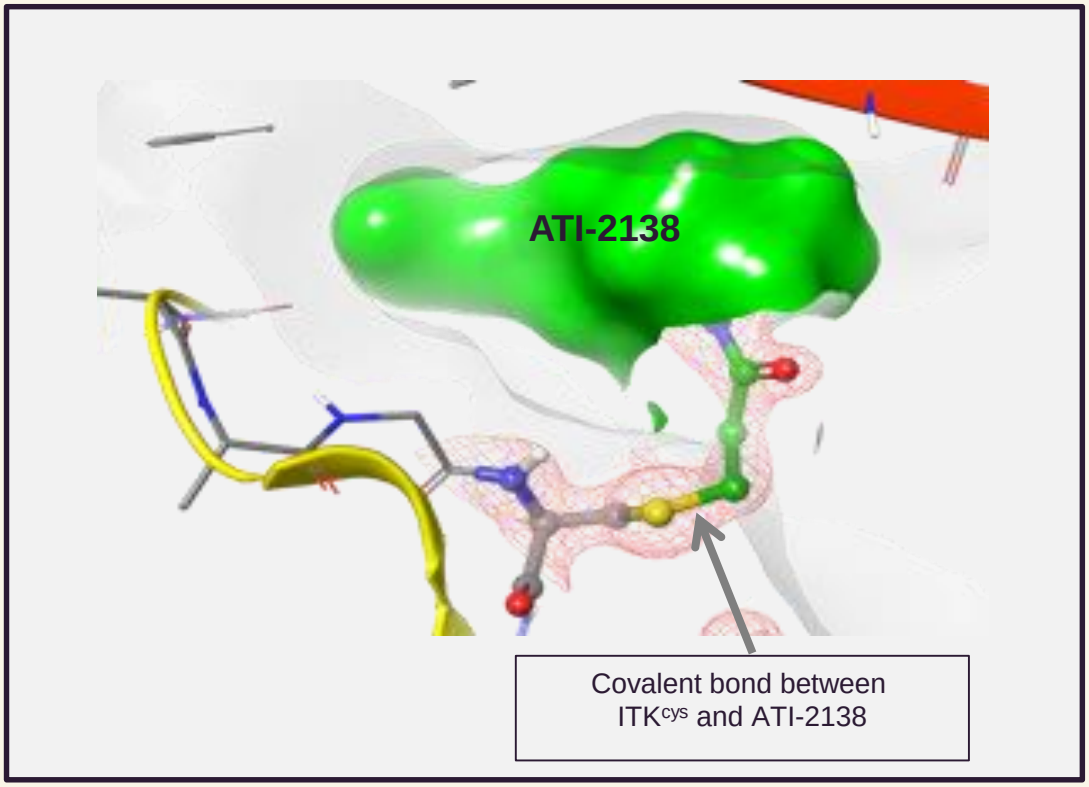
ATI-2138: Covalent ITK/TXK/JAK3 (ITJ) Inhibitor

- ATI-2138 (investigational compound) covalently blocks ITK/TXK/JAK3*
  - ✓ ITK/TXK required for T-cell receptor (TCR) signaling
  - ✓ JAK3 required for γc cytokines (IL-2/4/7/9/15/21)
  - ✓ Targeting both with a single drug may produce synergistic efficacy - expected to have few off-target effects
  - ✓ PD effects persist after plasma clearance
  - ✓ Efficacy demonstrated in rat arthritis and mouse colitis
- ATI-2138 is selective for T-cell signaling
  - ✓ Drugs like cyclosporine (CsA) inhibit calcineurin which is widely expressed
  - ✓ ATI-2138 targets unique kinases expressed only in immune cells and may provide more complete inhibition of the TCR without dose limiting toxicities
- ATI-2138 may potentially treat any T-cell mediated autoimmune disease
- Next planned milestones
  - ✓ IND submission in 4Q20/1Q21
  - ✓ First In Human - 1H 2021



* Data on file

ATI-2138 is a Potent Covalent Inhibitor



Co-Crystal Structure of ATI-2138/ITK - shows ATI-2138 covalent binding to ITK

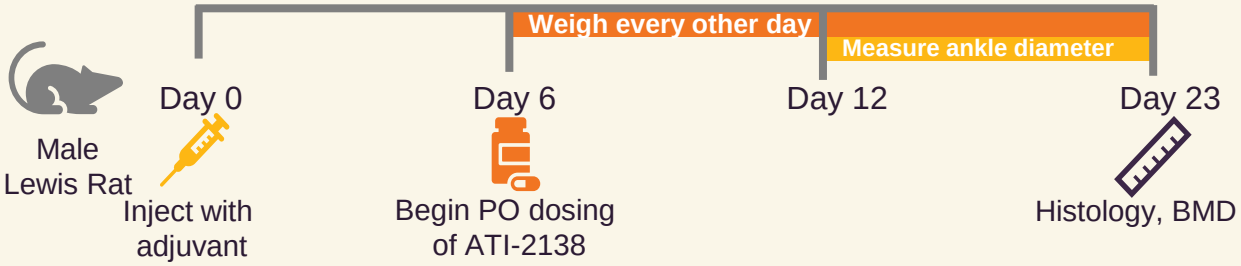
Cellular Inhibition of JAK and ITK/TXK

Assay Description	ATI-2138 IC_{50} (nM)	Assay
ITK/TXK activity	7	Jurkat pPLCγ-1
JAK1/3 activity	20	PBMC pSTAT-5
Both ITK/TXK and JAK3	13	HWB αCD3/IL15 IFNγ
BTK activity	52	Ramos pPLCγ-2

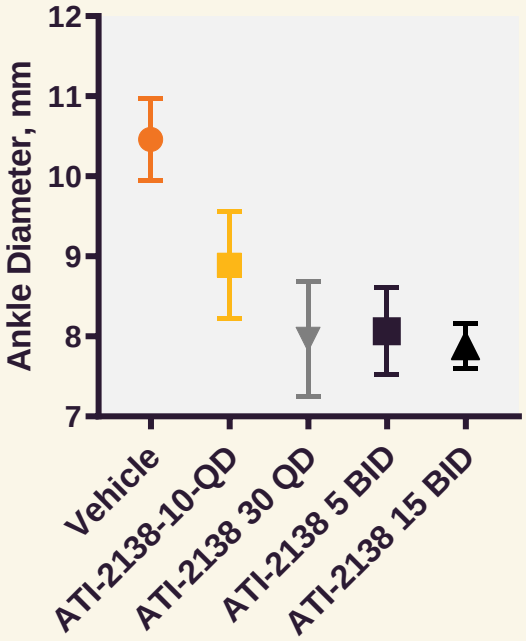
ATI-2138 potently inhibits ITK/TXK and JAK3 in cells and in whole blood

* Data on file

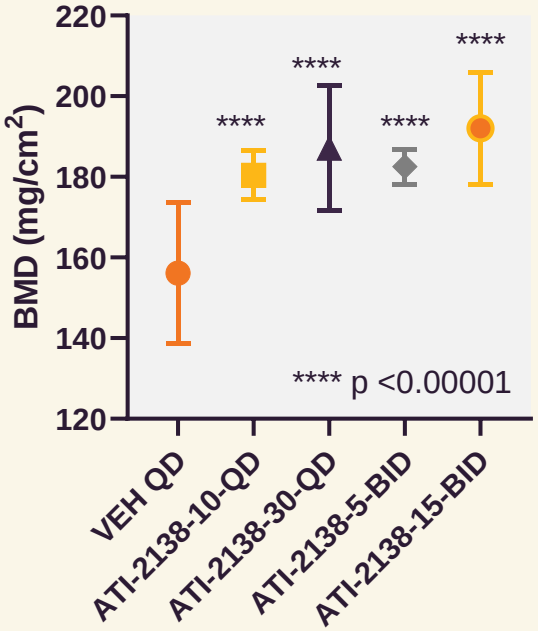
Rat Adjuvant Induced Arthritis (AIA) Model:
ATI-2138 Reduced Inflammation and Protected Bone

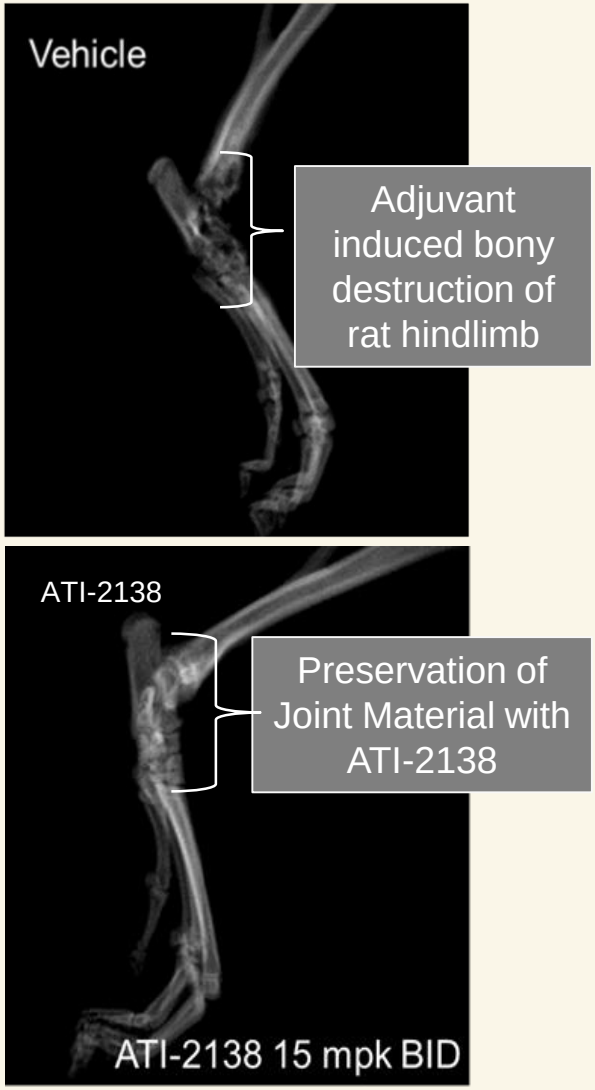


Day 23 ankle diameter



ATI-2138 bone mineral density in rat AIA study

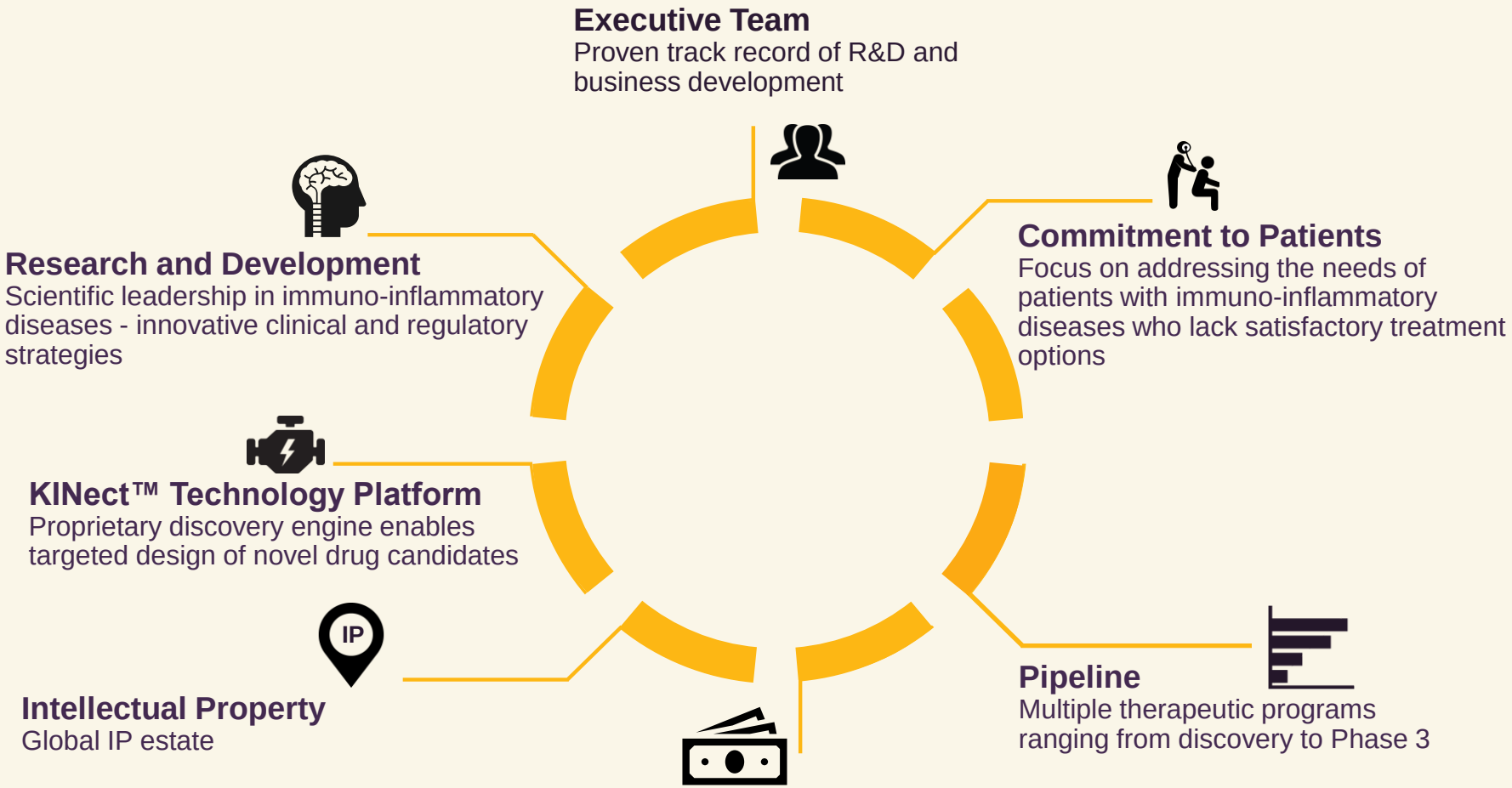




ATI-2138 reduced inflammation and bone mineral density loss

* Data on file

Biopharmaceutical Company



Catalysts

Milestone	2020				2021	
	1Q	2Q	3Q	4Q	1Q	2Q
ATI-450 (MK2 Inhibitor)						
Phase 1 Data (SAD/MAD)	✓					
Initiate Phase 2a Trial in Rheumatoid Arthritis						
Phase 2a Data in Rheumatoid Arthritis						
ATI-1777 (Topical Soft-JAK Inhibitor)						
Submit IND						
Initiate Phase 1/2 Trial						
ATI-2138 (ITK/TXK/JAK3 Inhibitor)						
Submit IND						
Initiate Phase 1/2 Trial						

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EMPOWERING PATIENTS THROUGH
KINOME INNOVATION

THANK YOU

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