EMPOWERING PATIENTS THROUGH

KINOME INNOVATION

ATI-450-RA-201
ATI-450-PKPD-102

January 2021

Preliminary Topline Analyses

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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 ATI-450 as a potential treatment for rheumatoid arthritis and the clinical development of ATI-450, including the further development at higher doses. 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, risks and uncertainties associated with preliminary trial results varying from final results, 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, 2019, Aclaris’ Quarterly Report on Form 10-Q for the quarter ended September 30, 2020 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

Founded and Led by Physicians and Scientists

- World class ex-Pfizer (kinase) and ex-GSK (immunology) leadership
- Kinome experts skilled at developing kinase targeted medicines

KINect™ PLATFORM

Proprietary Kinase Discovery Engine

- Versatile 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)

ATI-450 - MK2i

- Oral anti-TNFα, anti-IL1, anti-IL6

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

- Tissue specific therapy for the potential treatment of moderate-to-severe atopic dermatitis (AD)

ATI-2138 - ITK/TXK/JAK3i

- Oral dual inhibitor of T-cell and cytokine receptors

Development of Small Molecule Therapeutics for Immuno-inflammatory Diseases

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Experienced R&D Leadership Team

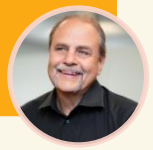
Proven Track Record in Immunology and Inflammation

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

David Gordon
Chief Medical Officer

- Former Executive Director, Pfizer Inflammation Research and Leader of Global Kinase Technology Team
- >95 publications and patents (>30 total on kinases)

Joseph Monahan, PhD
Chief Scientific Officer



- 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

Walter Smith
Scientific & BD Consultant

- Former Research Fellow and Director, Pfizer Chemistry
- >100 publications and patents (15 total on kinases)
- Project Lead for PFE JAK Program

Jon Jacobsen, PhD
VP, Chemistry

- Immunologist/drug discovery leader at pharma (Pfizer & biotech)
- Validated JAK 1/3 as target for transplant/RA/psoriasis, leading to approval of XELJANZ®

Paul Changelian, PhD
VP, Biology

- 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

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

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

Gary DeCrescenzo
SVP, Pharm R&D

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Strategic Focus

Leverage Kinome Target Discovery to Address Unmet Needs

Advance the process of identifying and targeting key kinome-based enzymes involved in chronic inflammation and autoimmune disease.

Model, elaborate and assess compounds through a unique combination of our proprietary chemical library of kinase inhibitors, our expertise in structure-based drug design, and our custom kinase assays.

Validate newly created drug candidates through pathophysiologically-relevant custom assays that effectively translate to human diseases.

Leverage research and commercial partnerships to accelerate the clinical evaluation and potential impact of discovery platforms.

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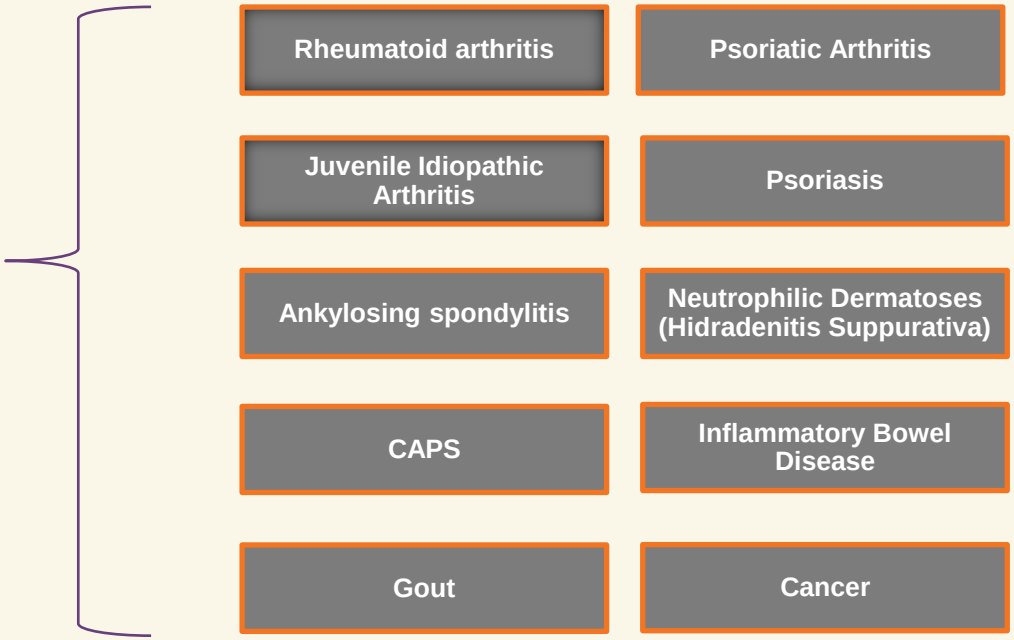
ATI-450: Investigational Small Molecule, Oral MK2 Inhibitor
Designed to Block the Targets of Broadly-Used Biologics

- **MK2* drives pro-inflammatory cytokine expression**
- **By inhibiting multiple cytokines, ATI-450 may be a potential treatment for multiple diseases**
- **Potential alternative to injectable, anti-cytokine biologics and JAK inhibitors for immuno-inflammatory diseases**

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



Global immunology market valued at >$77B in 2018[2]

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

1. Data on file.
2. Fortune Business Insights. Accessed January 18, 2021. https://www.fortunebusinessinsights.com/industry-reports/immunology-market-100657.

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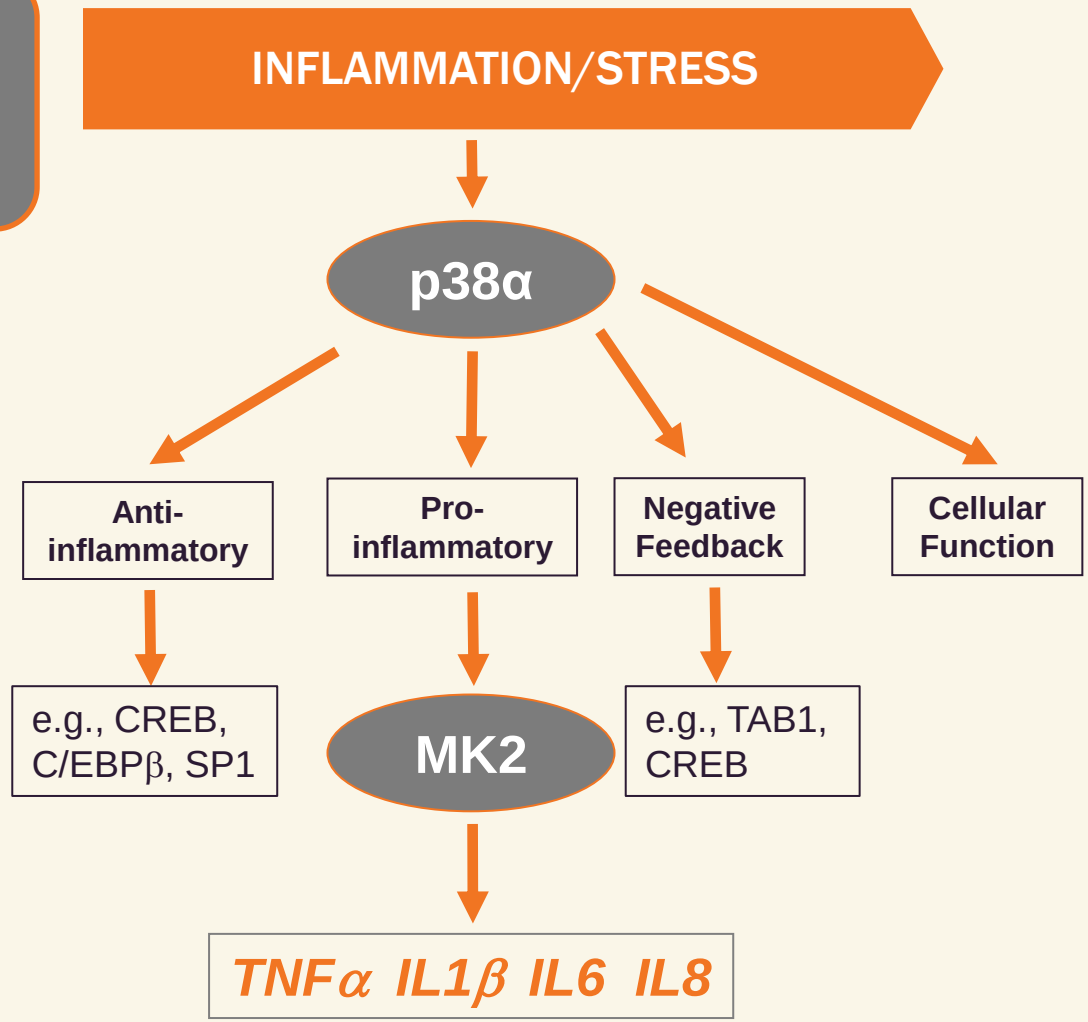
Evolution in Understanding a Well-Known Inflammatory Pathway
The Path From p38α to MK2

We believe MK2 is the optimal drug target in the p38 pathway to maximize anti-inflammatory efficacy and minimize toxicity

- Global p38α inhibitors have exhibited toxicity and/or lack of sustained efficacy in RA and IBD
  - Inability to dose escalate due to safety
  - Signaling network reprogramming
  - Downregulation of anti-inflammatory cytokines
- MK2 drives the proinflammatory node of this pathway while p38α phosphorylates over 60 substrates
- MK2 has been a high priority therapeutic target since 1999 but has proven very difficult to drug



* 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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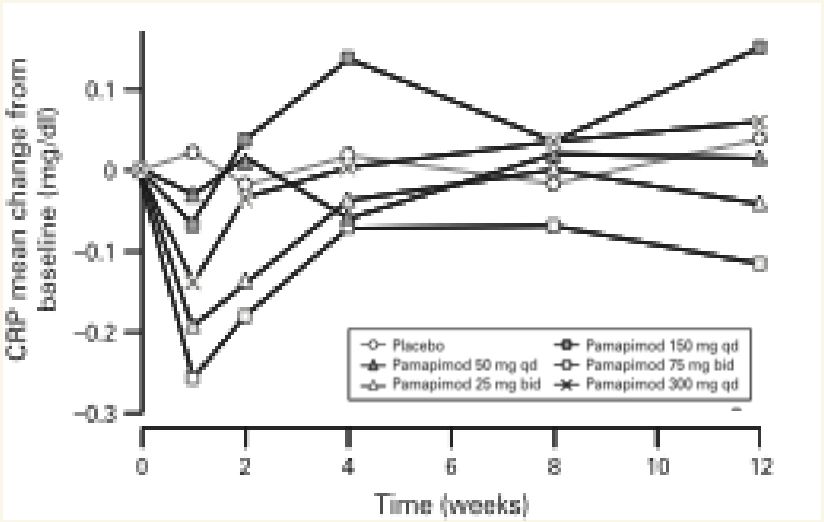
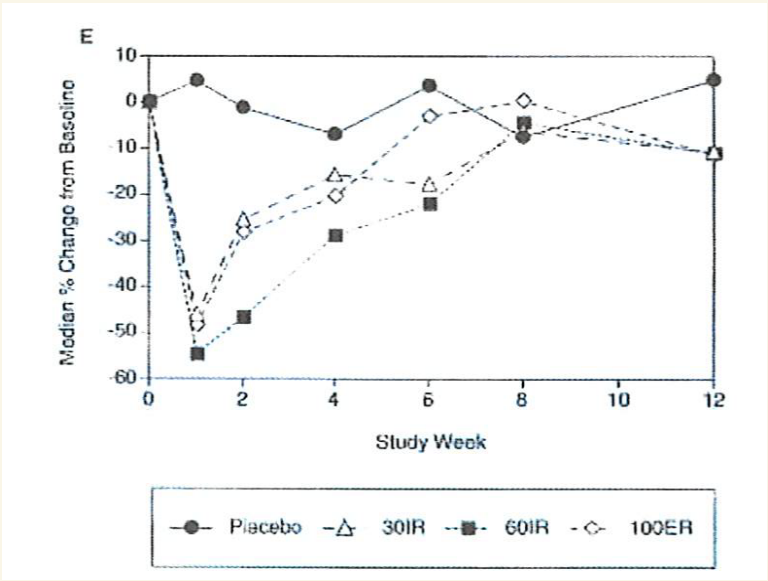
p38 Inhibitors: Tachyphylaxis in RA Clinical Trials
Transient CRP Reduction

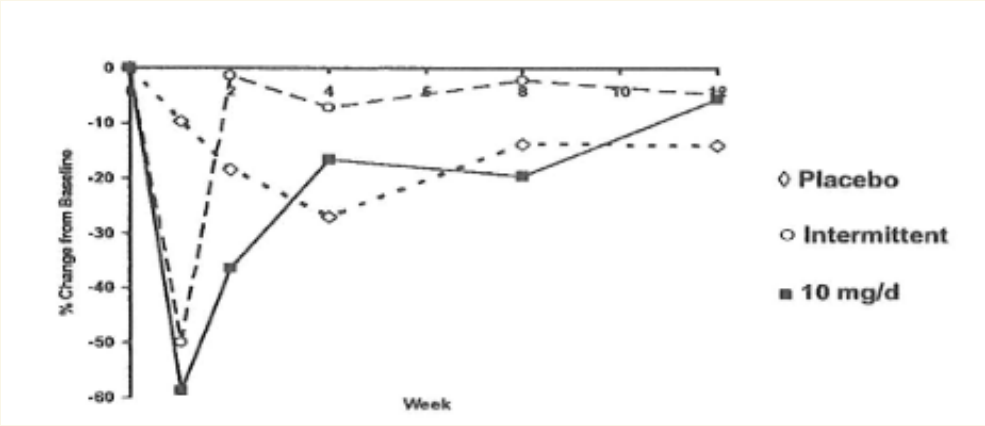
Pamapimod + MTX vs. Placebo + MTX[1]



SCIO-469 vs. Placebo[2]



304: VX-702 + MTX vs. Placebo + MTX[3]



Transient CRP reduction in multiple trials

1. Alten RE, et al. *Ann Rheum Dis.* 2010;69(2):364-367.
2. Genovese MC, et al. *J Rheumatol.* 2011;38(5):846-854.
3. Damjanov N, et al. *Arthritis Rheum.* 2009;60(5):1232-1241.

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Overview

- **ATI-450 development program consists of:**
  - Rheumatoid Arthritis
  - CAPS
  - COVID-19
  - MAD cohort extension (80mg BID, 120mg BID)

- **Today's update:**
  - Progress on RA-201: summary of topline data
  - MAD cohort extension (80mg and 120mg BID)

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ATI-450-RA-201
Preliminary Topline Data Analysis

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Trial Design

- Diagnosis of adult-onset RA (ACR/EULAR classification criteria)
- DAS28-CRP ≥3.2 defined as moderate to high disease activity
- Moderately to severely active RA defined by at least 4/28 tender and 4/28 swollen joints
- hsCRP ≥5 mg/L at screening
- Definitive intra-articular synovitis or osteitis defined as a score of 1 or greater on a Hand-Wrist MRI (using RAMRIS)
- Stable MTX dose (defined as 7.5 mg to 25 mg weekly) for at least 4 weeks prior to the screening visit

RANDOMIZATION (3:1)

ARM 1
ATI-450, 50 mg BID + MTX

ARM 2
Placebo, BID + MTX

12 weeks

Primary Objective: Safety

N-25 (to get 15 completers)

Secondary Objectives

- % change from baseline in hsCRP
- Mean change from baseline in DAS28-CRP
- Proportion of patients with DAS28-CRP below 2.6
- Mean change in RAMRIS assessments of synovitis or osteitis
- Proportion of patients with ACR 20/50/70

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Key Demographics

Parameter	Placebo (n=3) Median (Min – Max)	ATI-450 (n=16) Median (Min – Max)
Age (years)	53 (50 – 63)	59.5 (32 – 65)
Gender	(F) 3/3 (100%) (M) 0/0 (0%)	(F) 11/16 (68.75%) (M) 5/16 (31.25%)
Weight (kg)	105.4 (82.2 - 109.2)	88.15 (52.7 - 141.5)
Duration of Disease	1.6 (0.3 - 20.6)	6.45 (0.3 - 33.4)
hsCRP (mg/L)	21.3 (12.6 - 31.2)	11.7 (2.6 - 29.5)
DAS-28	5.3 (5.3 - 6.7) Mean (SD): 5.77 (0.808)	5.65 (3.9 - 7.4) Mean (SD): 5.71 (0.937)

- 19 subjects randomized (16 ATI-450, 3 PBO)
- Broad range of disease duration 0.3 – 33.4 years
  - High hsCRP despite long history and multiple treatment options

- 2 Withdrawals
  - Placebo: subject required prohibited meds for musculoskeletal pain
  - ATI-450: subject evaluated for palpitations and elevated CPK – no cardiac event

* Data on file

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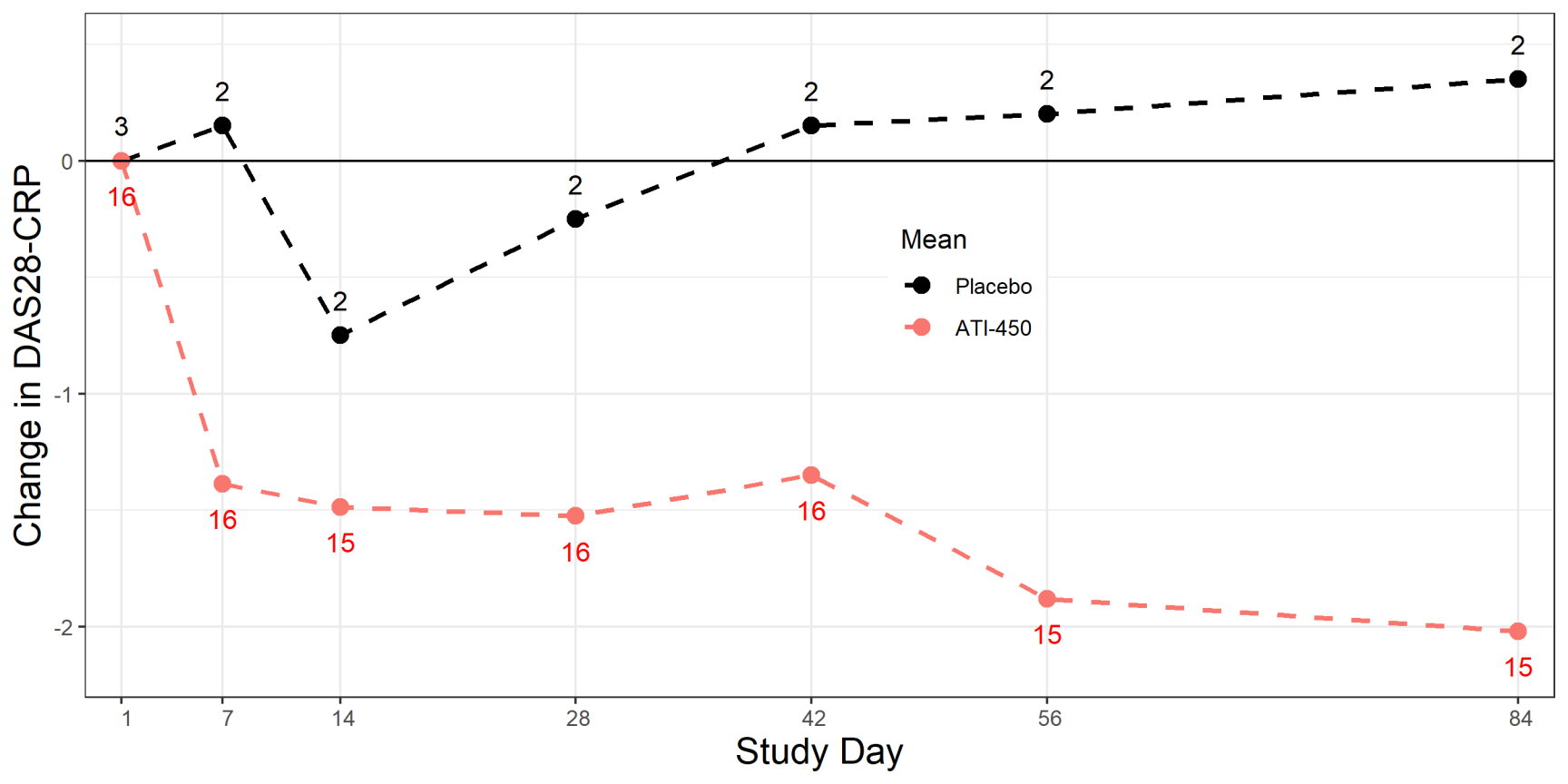
DAS28-CRP
Mean Change From Baseline



Numbers on lines = no. of subjects at each timepoint

* Data on file

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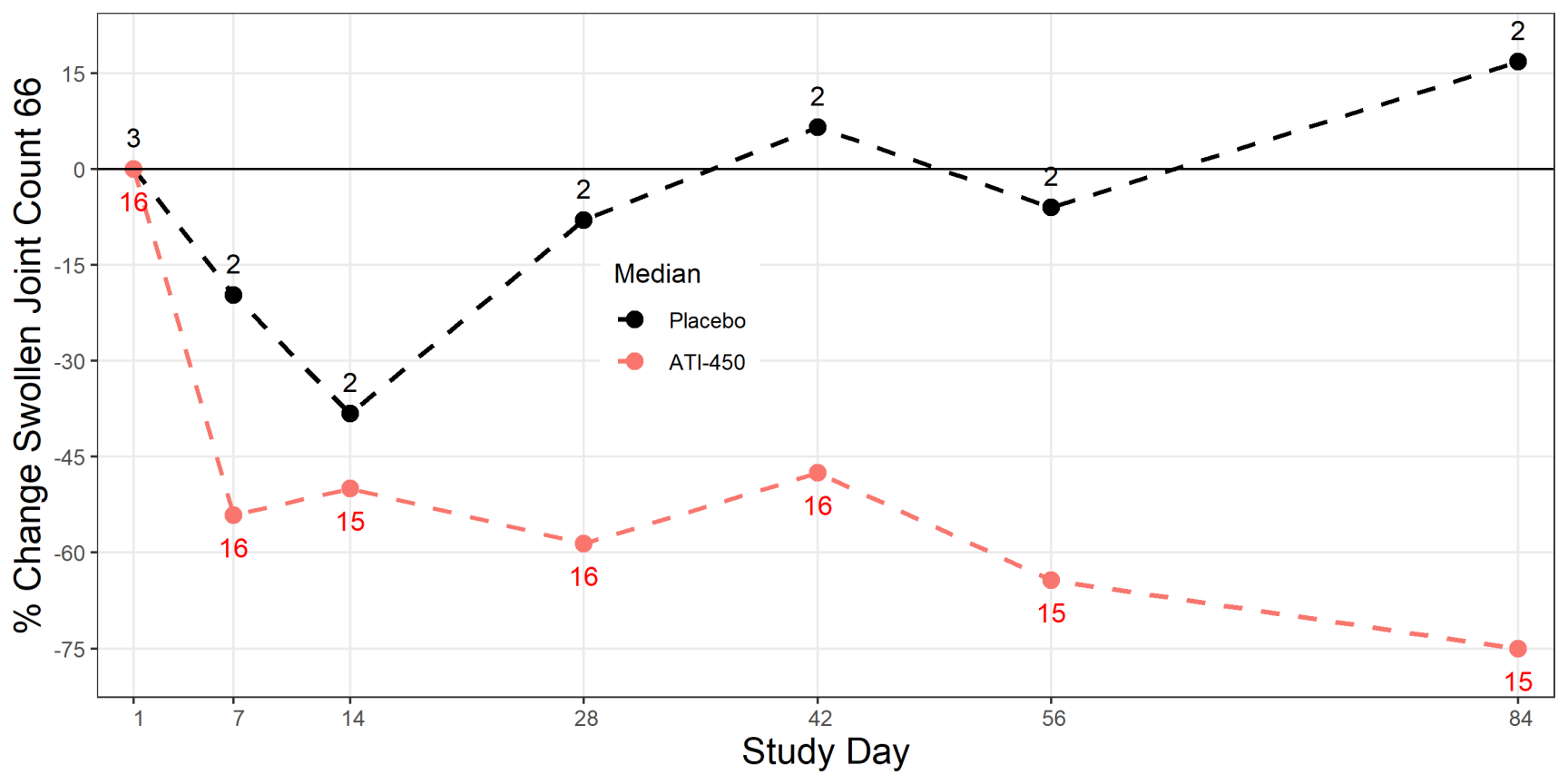
Swollen Joint Count
Median Percent Change From Baseline



Numbers on lines = no. of subjects at each timepoint

* Data on file

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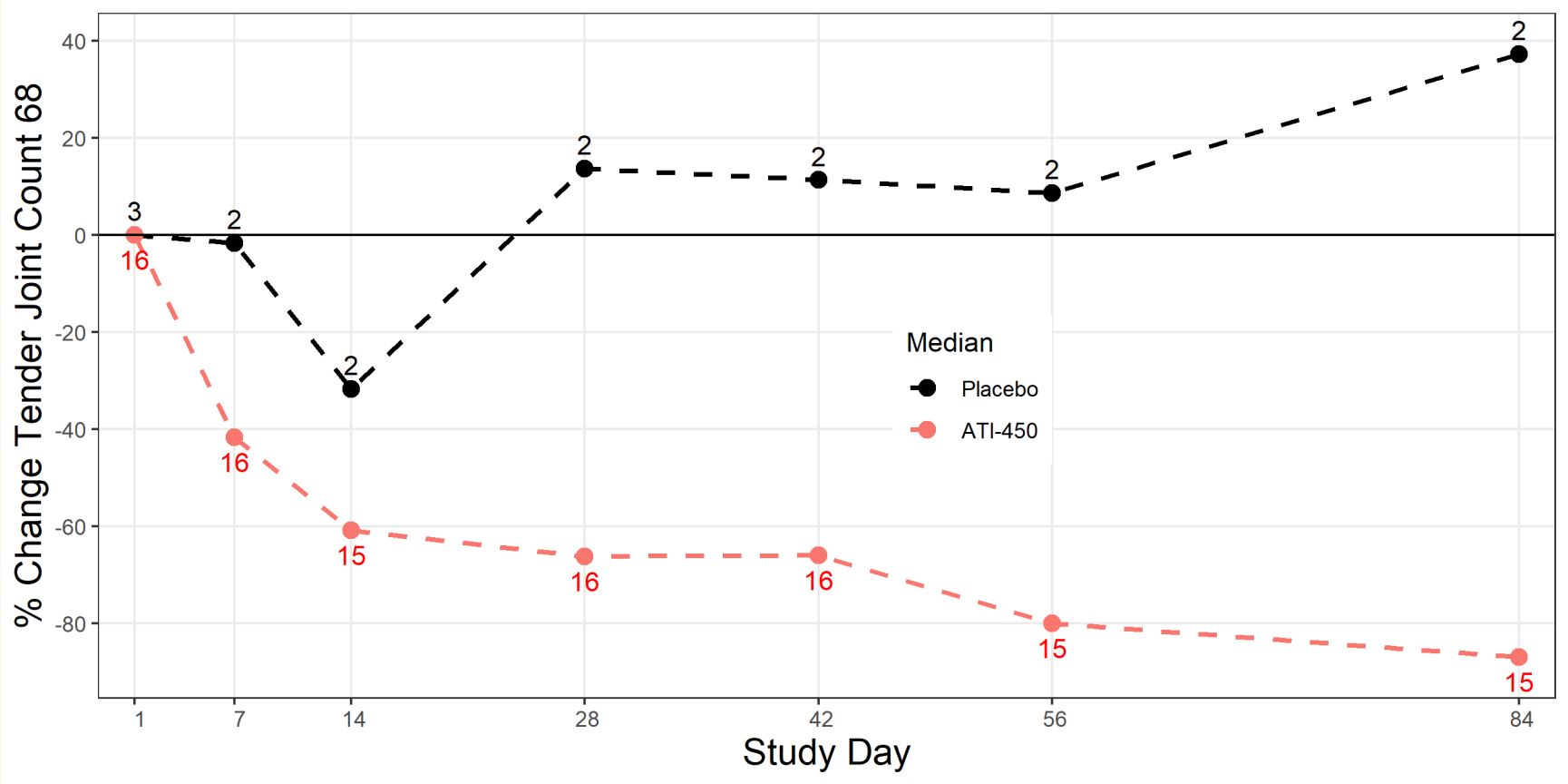
Tender Joint Count
Median Percent Change From Baseline



Numbers on lines = no. of subjects at each timepoint

* Data on file

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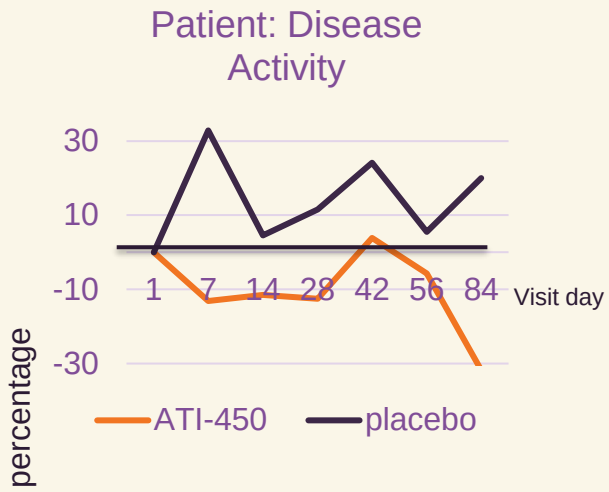
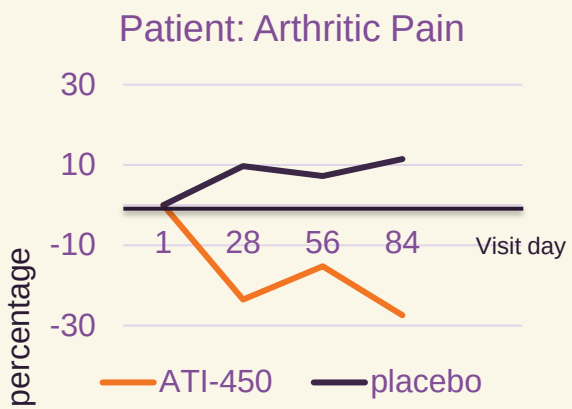
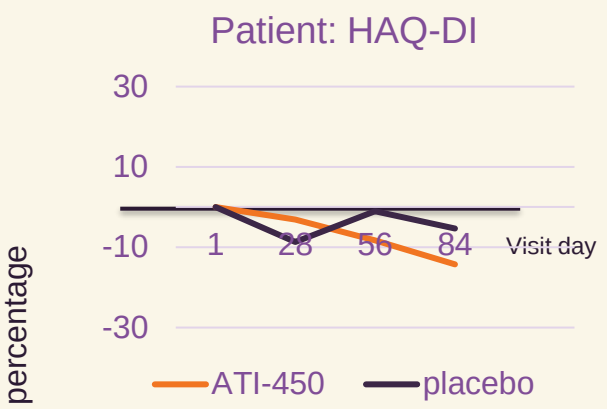
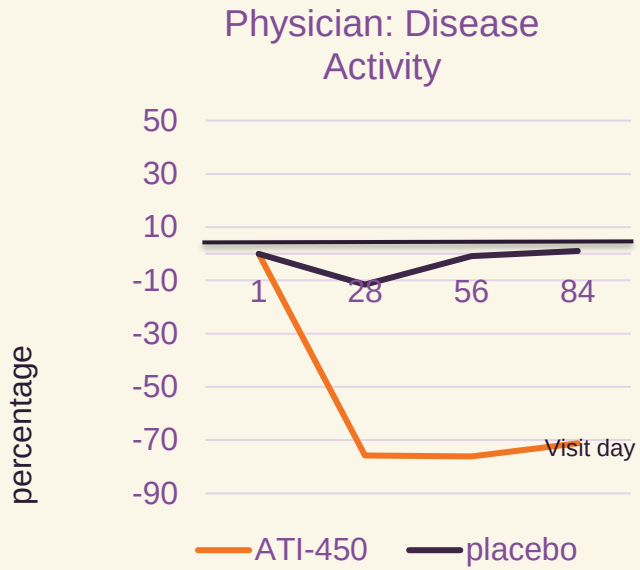
Subjective Physician & Patient VAS Scores

Median Percent Change









* Data on file

HAQ-DI = Health Assessment Questionnaire-Disability Index

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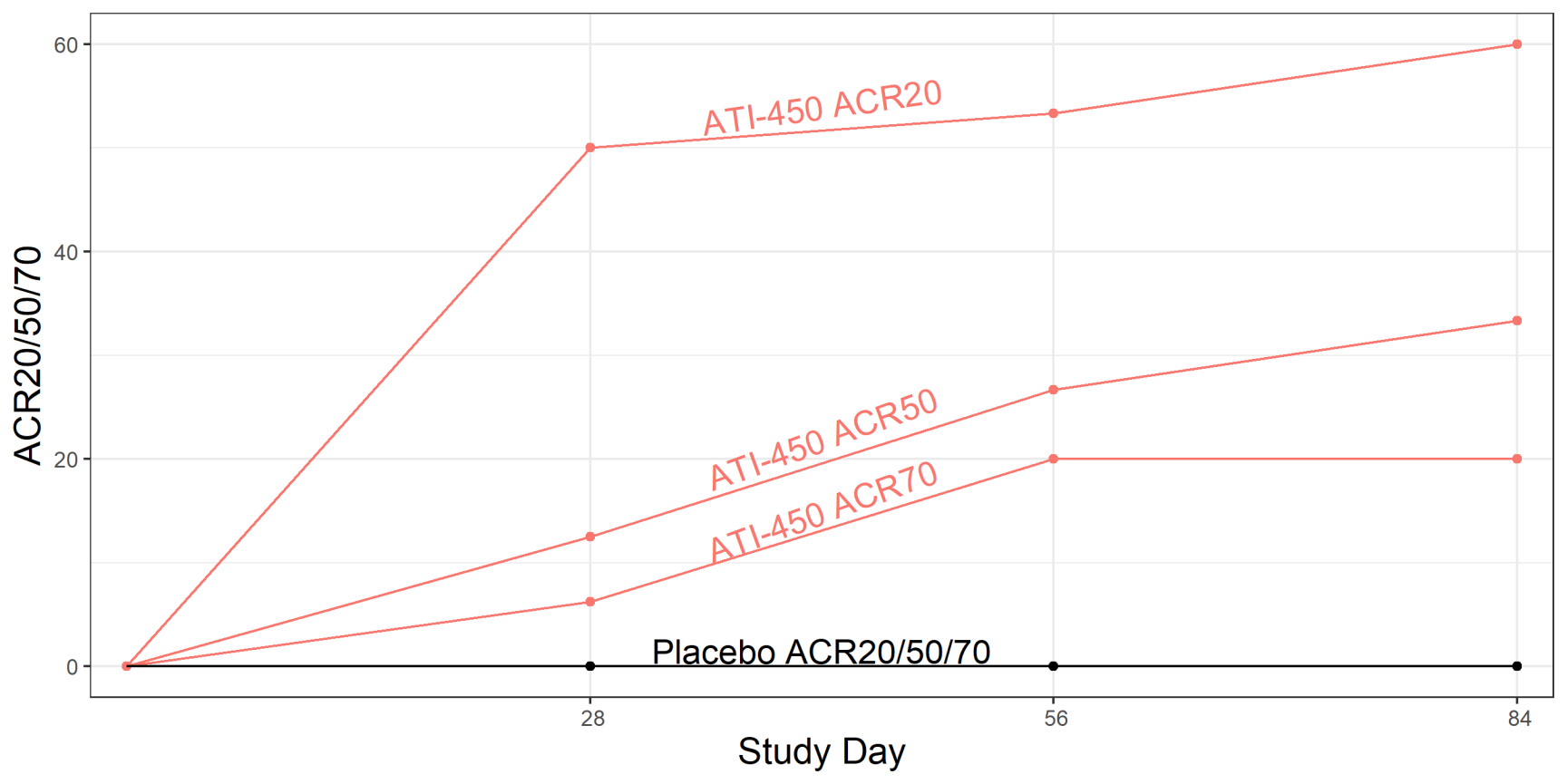
ACR20/50/70: *Responder Analysis over time*



* Data on file

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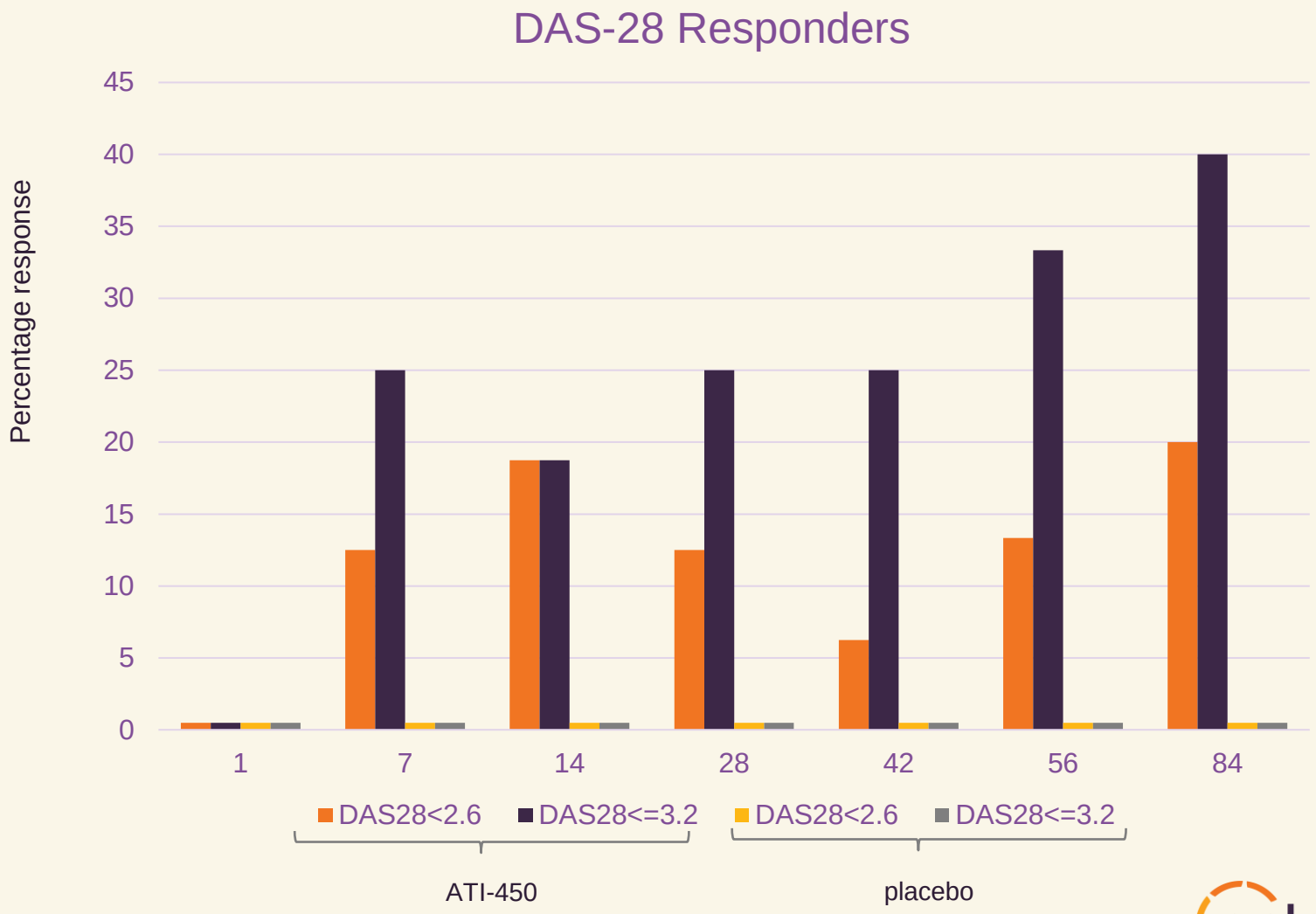
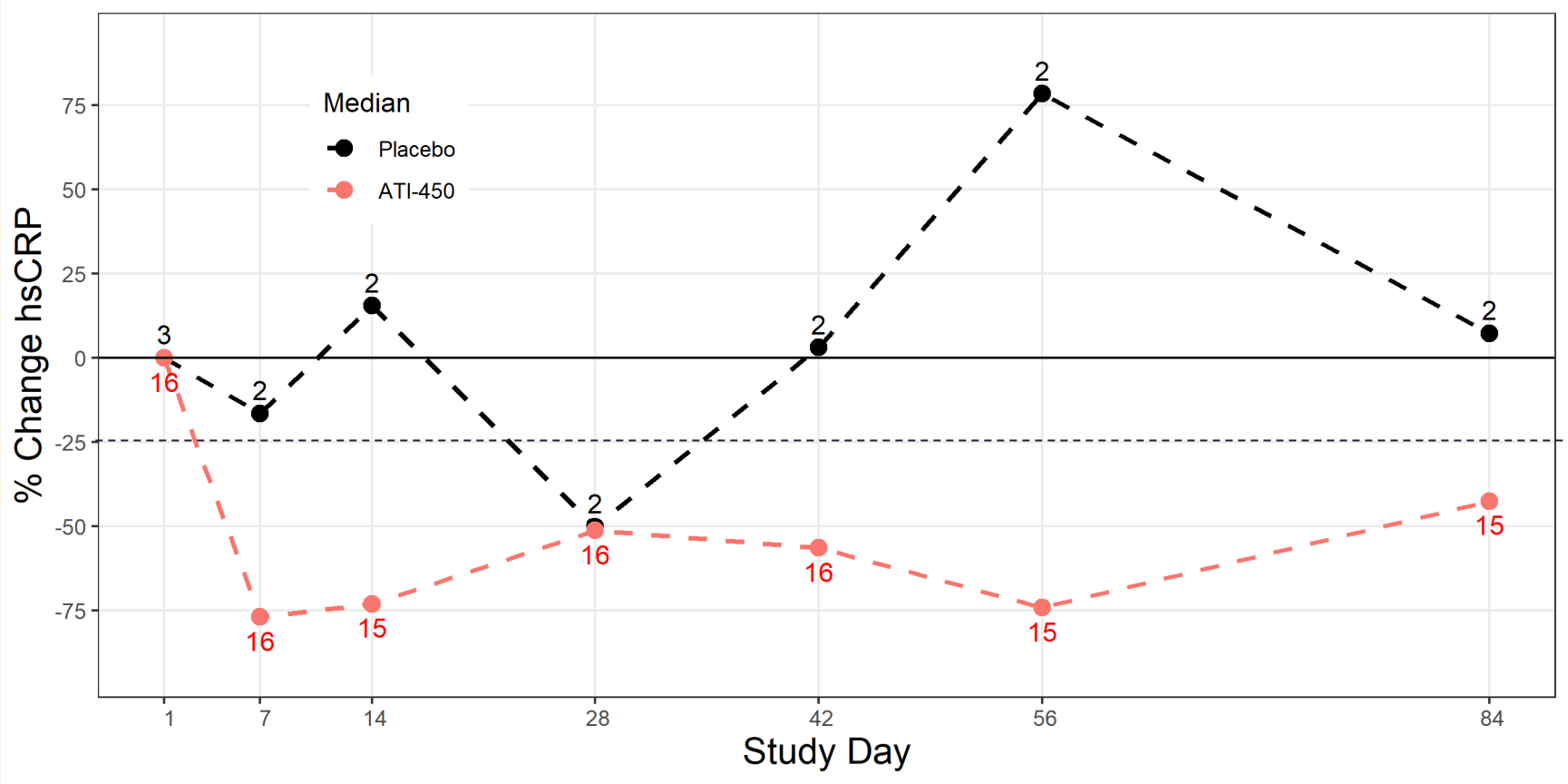
DAS28-CRP: *Responder Analysis over time*



* Data on file

hsCRP (mg/L)
Median Percent Change From Baseline



Numbers on lines = no. of subjects at each timepoint

* Data on file

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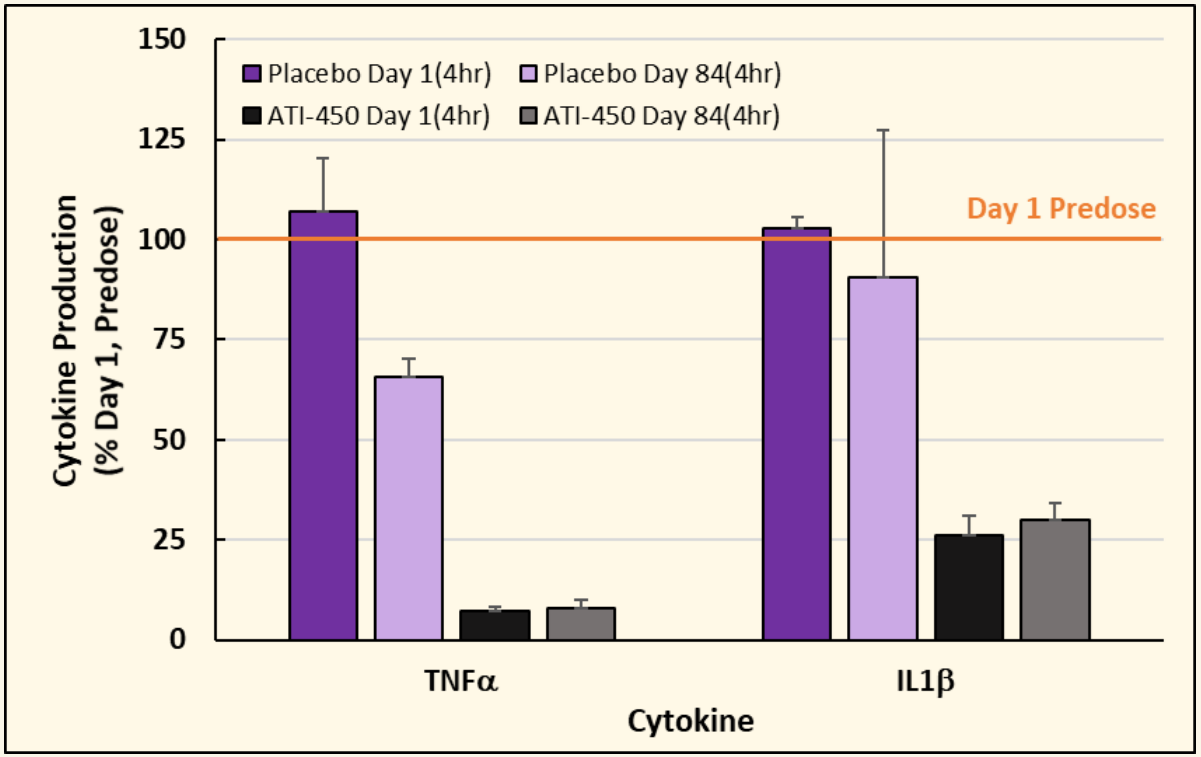
RA Patients Treated with ATI-450 for 12 Weeks
Ex Vivo LPS-Stimulated Cytokines Day 1 vs Day 84

Hypothesis: p38 transient efficacy (tachyphylaxis) may be associated with feedback loops and pathway reprogramming. Selectively targeting MK2 inhibition circumvents these issues through selective downstream pathway blockade.



Durable Dependence on MK2 for Cytokine Production

Interim Data N=11 Active, 2 Pbo

* Data on file as of December 10, 2020.

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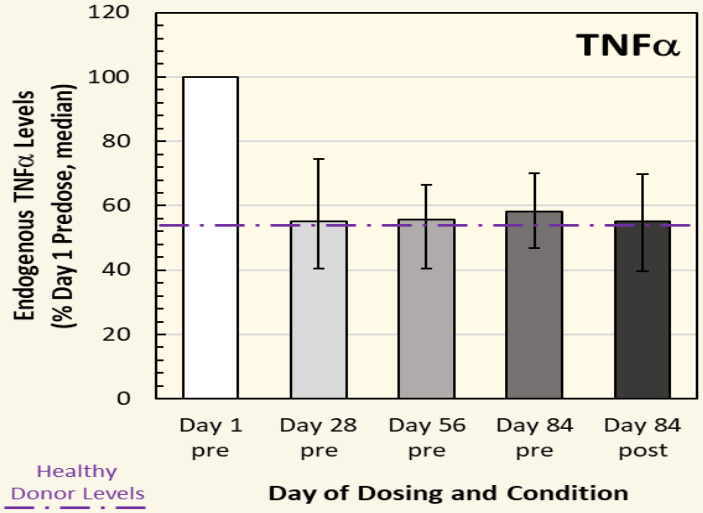
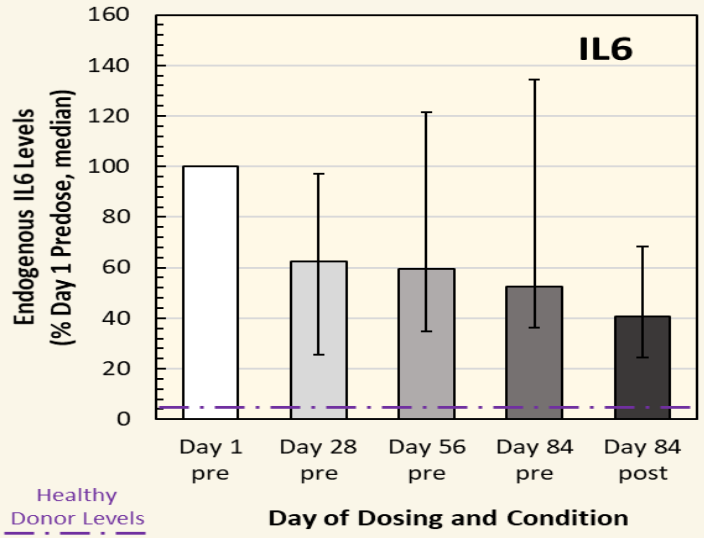
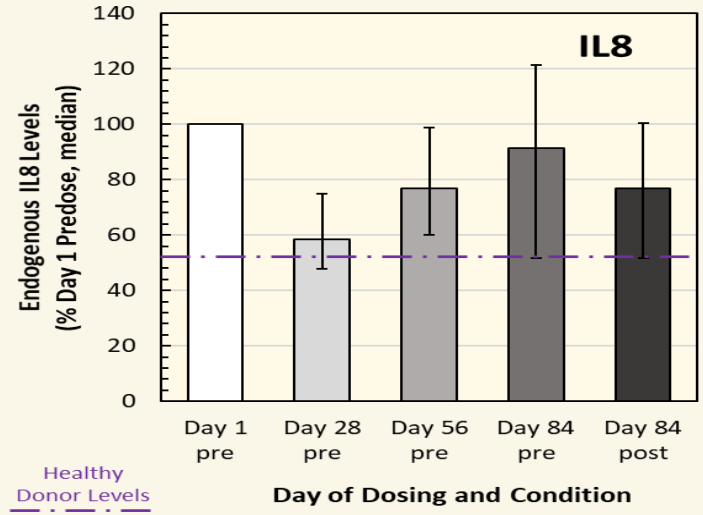
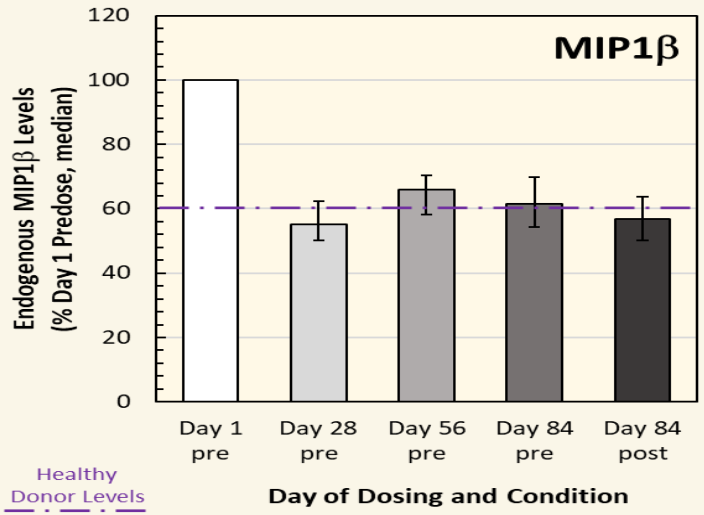
Impact of ATI-450 on Endogenous Plasma Cytokine Levels in RA-201

TNFα, IL6, IL8 and MIP1β









- Cytokines with endogenous levels <0.5 pg/ml predose:IL1β, IL10, IL4 and GM-CSF

* Data on file

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Adverse Events: Subjects with at least one event

	ATI-450 50 mg BID (N = 16)		Placebo (N = 3)	
Preferred Term	**Mild n(%)**	**Moderate n(%)**	**Mild n(%)**	**Moderate n(%)**
Blood cholesterol increased	1(6.25)	0		
Blood creatine phosphokinase increased	0	1(6.25)		
Constipation	1(6.25)	0		
Dental caries			1(33.33)	0
Ear infection	1(6.25)	0		
Electrocardiogram abnormal	1(6.25)	0		
Essential hypertension	0	1(6.25)		
Hyperlipidaemia	0	1(6.25)		
Hypokalaemia	0	1(6.25)		
Ligament sprain	1(6.25)	0		
Low density lipoprotein increased	1(6.25)	0		
Mouth ulceration	1(6.25)	0		
Muscle strain			0	1(33.33)
Palpitations	1(6.25)	0		
Rash erythematous	1(6.25)	0		
Sinusitis	0	1(6.25)		
Skin abrasion	1(6.25)	0		
Urinary tract infection	0	2(12.5)		
Ventricular extrasystoles	1(6.25)	0		
White blood cell count increased	1(6.25)	0		

- No Serious Adverse Events (SAE)
- No Severe Adverse Events
- ATI-450: one subject withdrew - evaluated for palpitations and elevated CPK – no cardiac event

* Data on file

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ATI-450-PKPD-102
Preliminary Topline Data Analysis

ATI-450-PKPD-102
Evaluation of Safety, PK and PD of Higher Doses

Background:

- ATI-450-PKPD-101: Phase 1 SAD/MAD trial in male and female healthy volunteers
  - No SAEs or AEs that led to discontinuation
  - All AEs were mild in severity and did not interfere with everyday activities
  - Trend of decrease in ANC observed; no correlation with clinical sequelae
  - Linear (dose-and time-independent) PK after multiple-dosing with terminal $t_{1/2}$ of ~9-12 hours; steady state by day 2
  - No meaningful impact on systemic exposure in the fed state
  - MTX PK was similar with or without ATI-450 exposure

- ATI-450-PKPD-102: Phase 1 MAD trial in male and female healthy volunteers
  - Same design to MAD portion of PKPD-101
  - 2 cohorts: 80mg, 120mg BID for 6.5 days
  - 10 subjects per cohort (8 active, 2 placebo)

* Data on file

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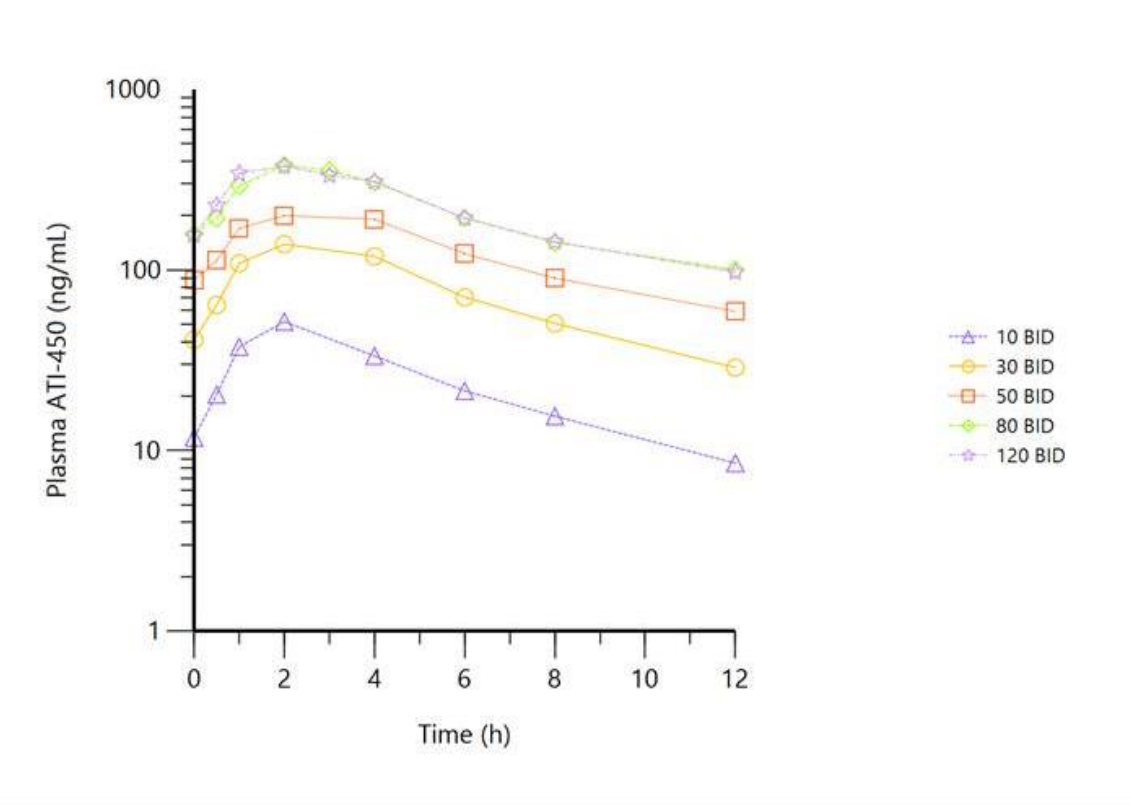
ATI-450-PKPD-101 & ATI-450-PKPD-102
Day 7 Steady State

- t½ 9-14 hours
- 80mg cohort dose proportional with previous cohorts
- No significant increased exposure in 120mg cohort



* Data on file

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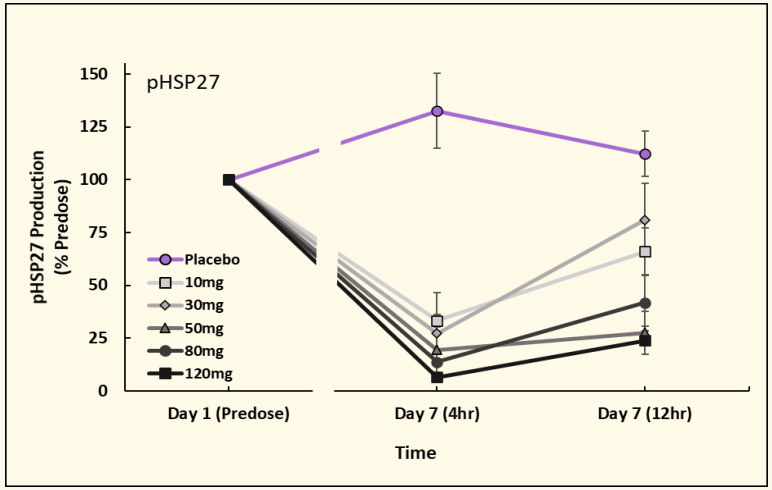
ATI-450-PKPD-101 & ATI-450-PKPD-102

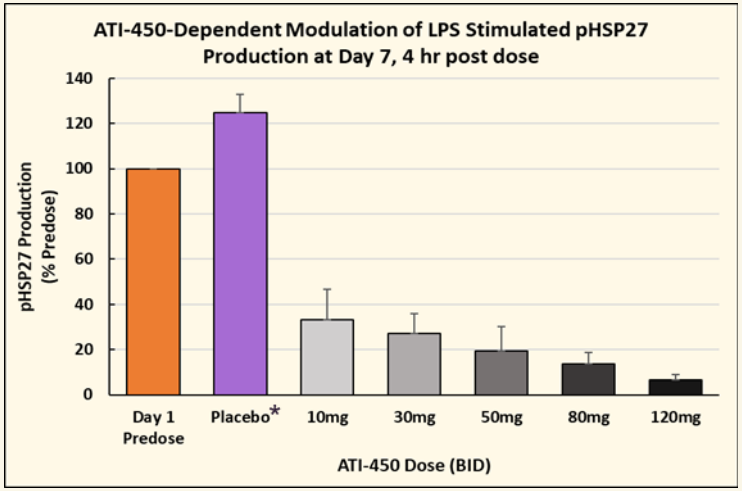
Ex vivo LPS stimulated pHSP27 and TNFα Day7 Peak and Trough

Day 7 Peak and Trough

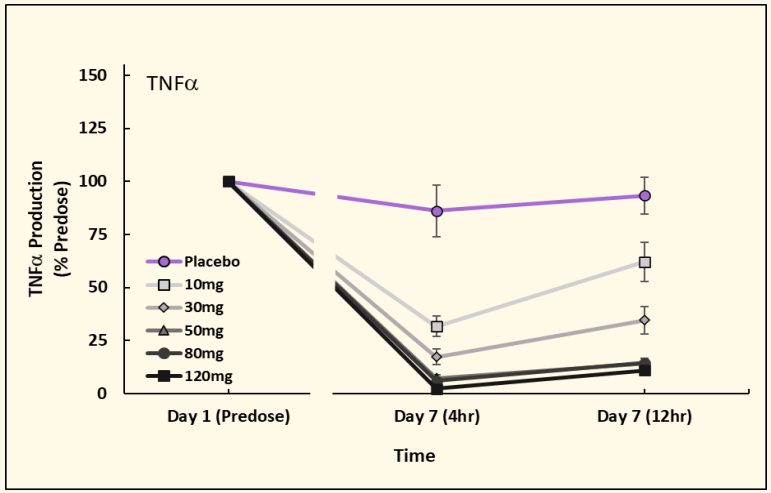
Dose Response Day 7 Peak

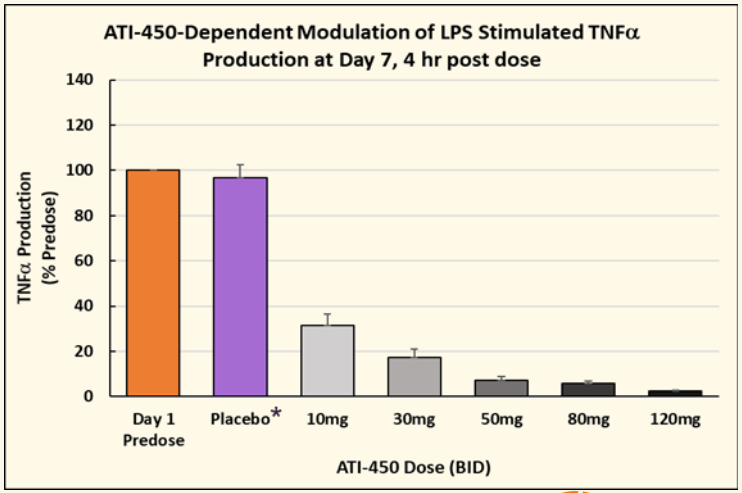
pHSP27





TNFα





(*) = All placebo samples (all time points)

* Data on file

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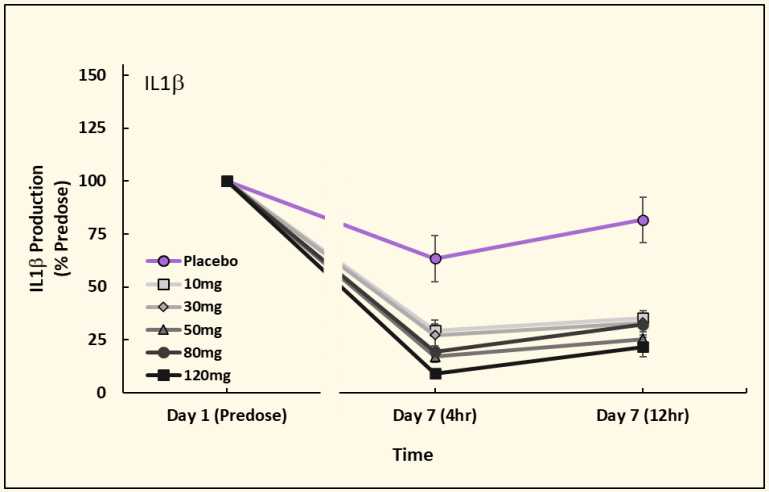
ATI-450-PKPD-101 & ATI-450-PKPD-102

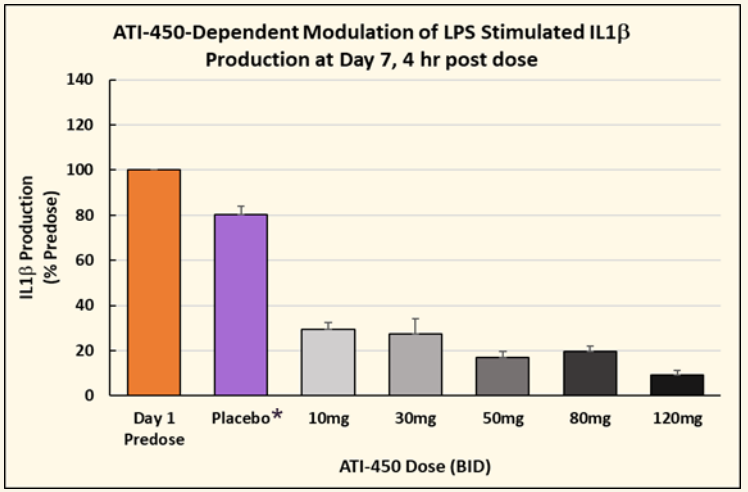
Ex vivo LPS stimulated IL1β and IL8 Day7 Peak and Trough

Day 7 Peak and Trough

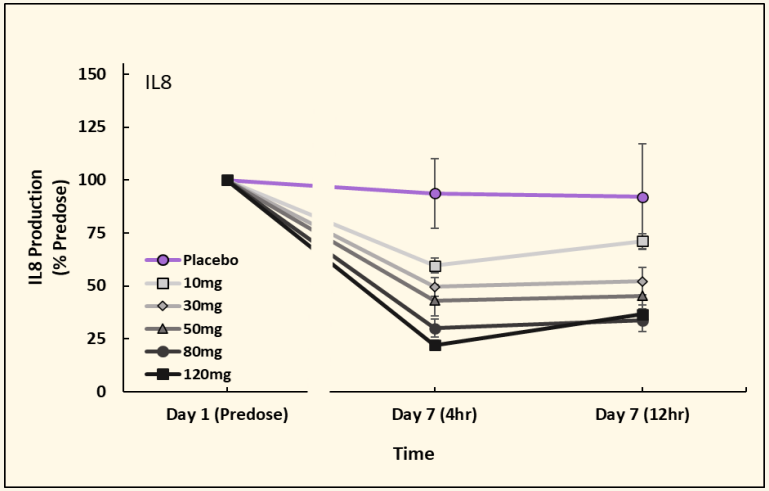
Dose Response Day 7 Peak

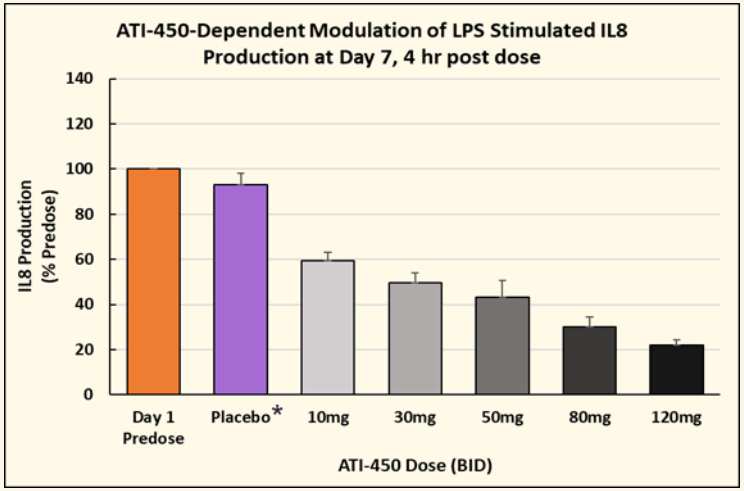
IL1β





IL8





(*) = All placebo samples (all time points)

* Data on file

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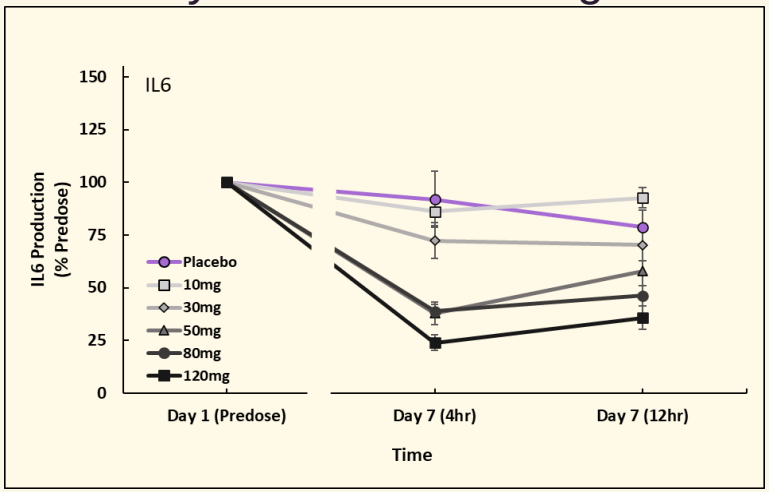
ATI-450-PKPD-101 & ATI-450-PKPD-102

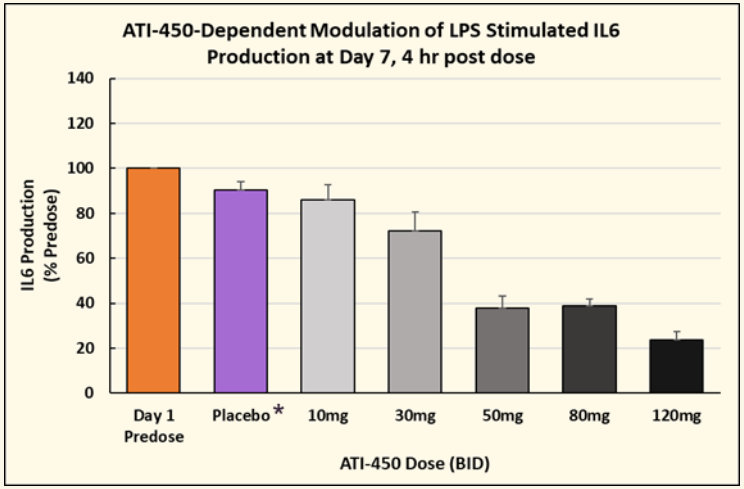
Ex vivo LPS stimulated IL6 Day7 Peak and Trough

IL6

Day 7 Peak and Trough



Dose Response Day 7 Peak



(*) = All placebo samples (all time points)

* Data on file

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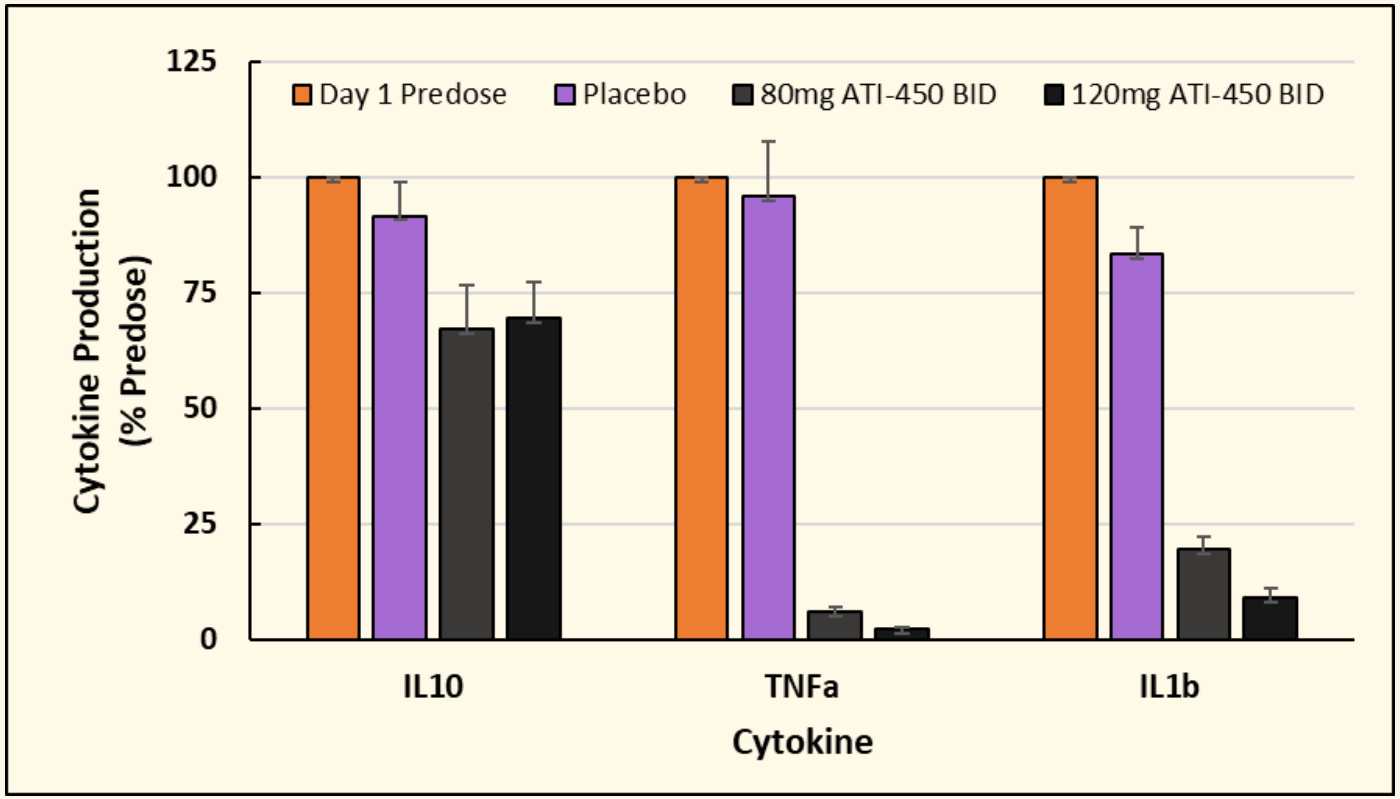
Phase 1 MAD Extension

Differential Modulation of Ex Vivo LPS-Stimulated IL10 vs. TNFα and IL1β by ATI-450 Day 7 (4 hr)



(*) = All placebo samples (all time points)

The anti-inflammatory cytokine, IL10, was only modulated approximately 30% at doses of ATI-450 that generated near maximal inhibition of proinflammatory cytokines (TNFα and IL1β)

* Data on file

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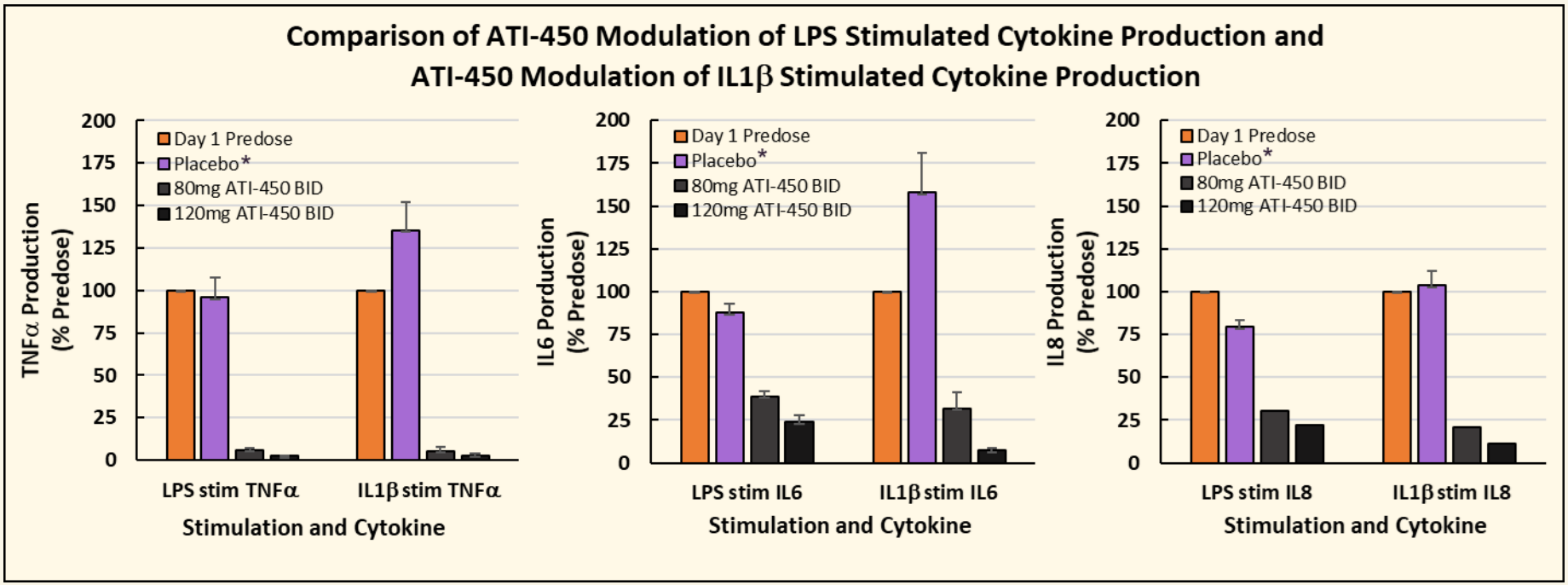
ATI-450 Phase 1 MAD Extension: 80mg and 120mg
Ex Vivo IL1β Stimulation of HWB Day 7 (4 hr)



(*) = All placebo samples (all time points)

ATI-450 potently inhibited ex vivo IL1β-induced proinflammatory cytokines, TNFα, IL6 and IL8

* Data on file

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ATI-450-PKPD-102
Adverse Events

	Cohort 1 80mg BID N=8	Cohort 1 Pbo N=2	Cohort 2 120mg BID N=8	Cohort 2 Pbo N=2	Severity
Total subjects with at least 1 AE	4 (50%)		8 (100%)	1 (50%)	
Headache#	2 (25%)		7 (88%)	1 (50%)	Mild
Dizziness+	2 (25%)		6 (75%)		Mild
Dry Skin*	1 (13%)		5 (63%)		Mild
Constipation	1 (13%)				Mild
Nausea			2 (25%)		Mild
Parasthesia			2 (25%)		Mild
Abdominal Pain			1 (13%)		Mild
Diarrhea			1 (13%)		Mild
Pharyngitis			1 (13%)		Mild

only 1st or 2nd day
+ 7 cases resolved on drug
* After stopping drug

- No SAEs
- No withdrawal for AEs
- No significant ECG, Laboratory findings

* Data on file

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Topline Analyses Summary

- **Main objectives of POC trial were achieved**
  - Potent and durable clinical activity with 50mg BID
    - Rapid reduction in median percentage of tender and swollen joint count, which persisted
    - DAS28-CRP reduction persisted
    - ACR20/50/70 observed in 60%/33%/20% of treatment arm
    - hsCRP reduction maintained
  - ATI-450 was generally well tolerated
- **Positive Phase 1 trial (80 and 120mg BID)**
  - No dose limiting toxicity in phase 1
  - Incremental inflammatory cytokine suppression
  - Pharmacokinetics data continue to support dosing flexibility (QD or BID)
  - Pharmacodynamic data provide rationale for evaluating activity at 80-120mg BID
- **Next steps**
  - Planning for Phase 2b program initiated

* Data on file

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