EMPOWERING PATIENTS THROUGH KINOME INNOVATION

Zunsemetinib (ATI-450) Phase 2b Rheumatoid Arthritis Trial Top-line Results

November 13, 2023

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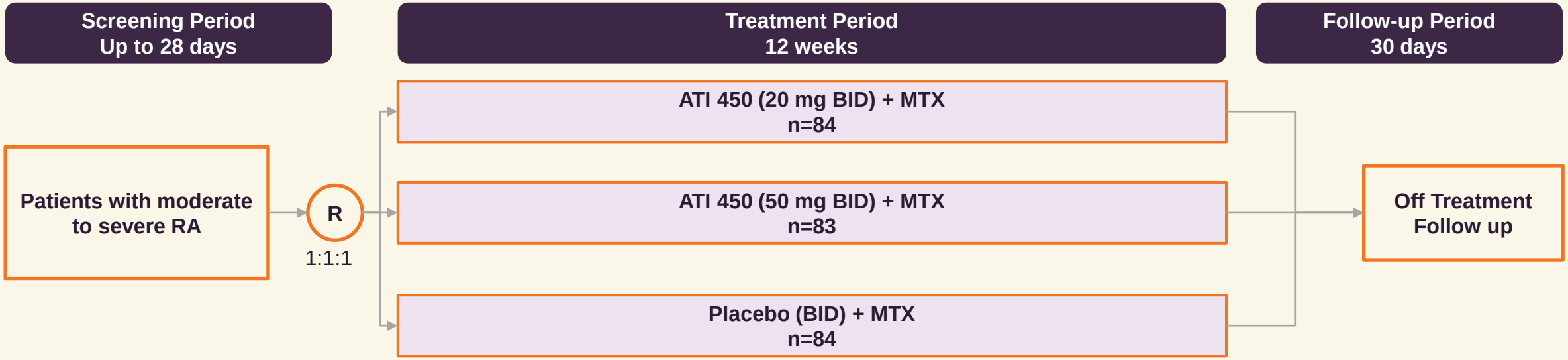
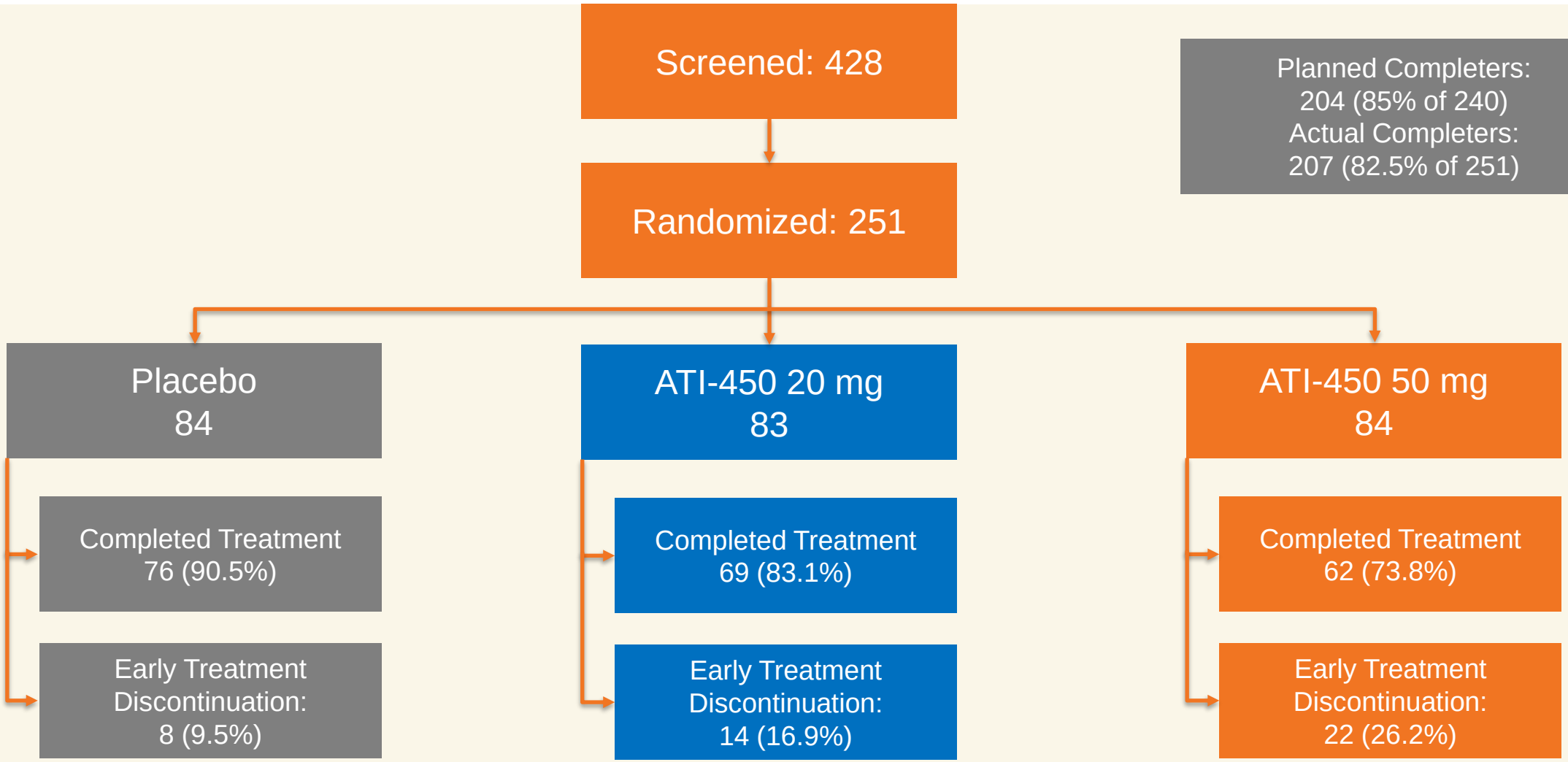
Trial Design



Assessment	Baseline	Week 1	Week 2	Week 4	Week 6	Week 8	Week 12
Tender and Swollen Joint Count	X	X	X	X	X	X	X
Patient Global Assessment	X	X	X	X	X	X	X
Physician Global Assessment	X	X	X	X	X	X	X
Patient pain, HAQ-DI	X			X		X	X
hsCRP	X	X	X	X	X	X	X
Pharmacodynamics (PD)	X			X		X	X

Patient Disposition: Treatment Arms Were Nearly Equal At Randomization with Higher Discontinuation Rate in Active Arms



Demographics: Arms Were Generally Balanced and Similar to Comparable Studies

Parameter	Placebo BID (N=84)	ATI-450 20 mg BID (N=83)	ATI-450 50 mg BID (N=84)
Age (mean)	55.5	55.9	55.8
Sex Male Female	 14.3% 85.7%	 25.3% 74.7%	 23.8% 76.2%
Race: White Black	 89.3% 3.6%	 91.6% 3.6%	 86.9% 2.4%
Weight (kg, Mean)	76.6	77.0	76.3
Height (cm, Mean)	164.3	166.1	165.9
BMI (Mean)	28.1	27.8	27.7

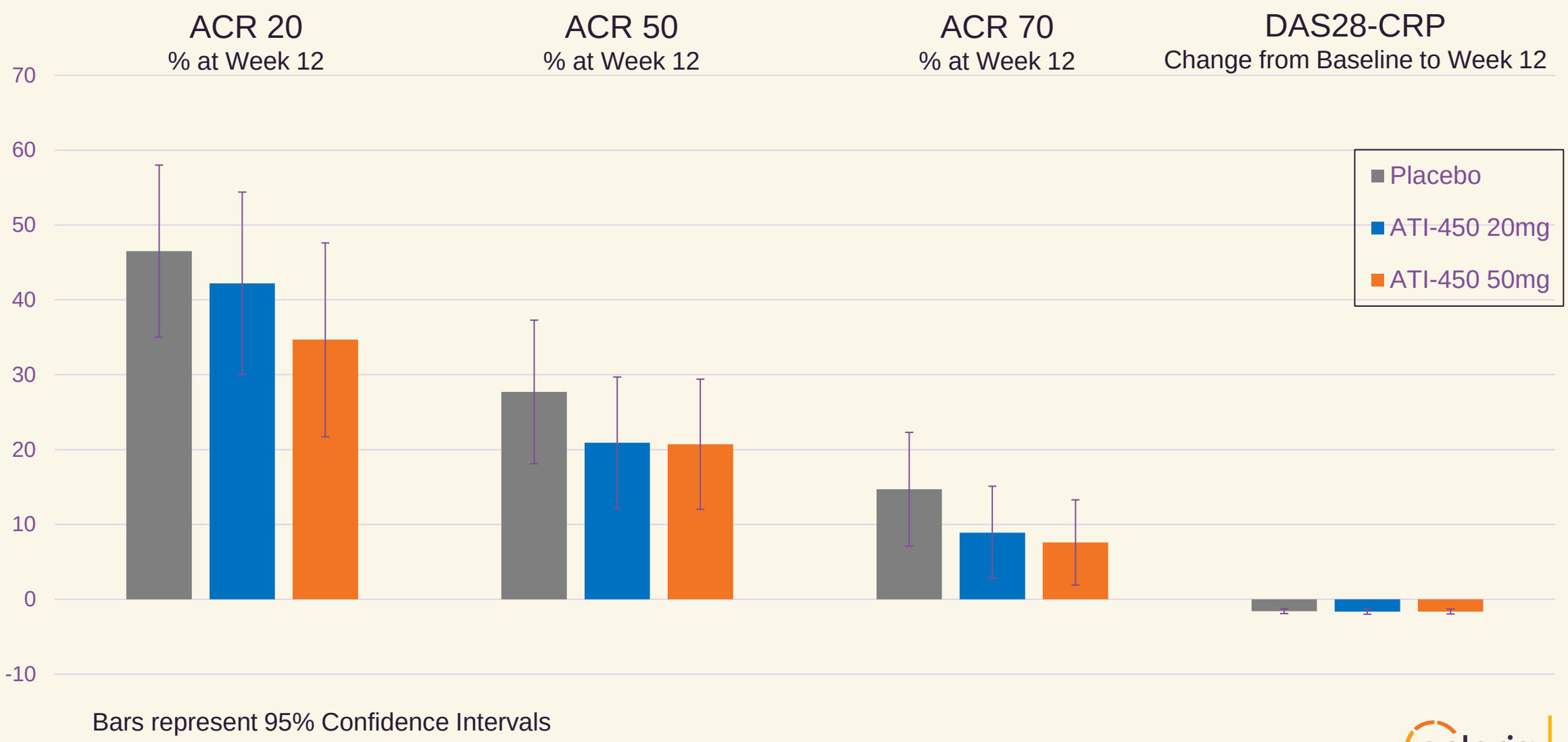
Baseline Disease Characteristics Were Generally Balanced Across Treatment Arms and Generally Similar to Comparable Studies

Parameter	Placebo BID (N=84)	ATI-450 20 mg BID (N=83)	ATI-450 50 mg BID (N=84)
Duration of RA (years)	7.8	8.0	6.9
Tender Joint Count (out of 68)	20	19	20
Swollen Joint Count (out of 66)	14	14	12
hsCRP	7.8	9.6	13.3
DAS28-CRP	5.4	5.4	5.5
HAQ Disability Index	1.4	1.4	1.4
Pain VAS	64.4	66.2	64.2
Patient Global VAS	66.1	66.5	65.1
Physicians' Global VAS	65.9	65.7	62.3
DAS28-CRP (Moderate/Severe)	32% / 67%	32% / 68%	36% / 64%
Rheumatoid Factor or anti-CCP Positive	88%	89%	89%
Prior Biologic or JAKi treatment	20%	20%	21%

High Discontinuation Rate with ATI-450 at the 50 mg Dose was Mainly Due to Adverse Events and Withdrawal of Consent

Reason	Placebo N = 84	ATI-450 20 mg N = 83	ATI-450 50 mg N = 84
All Causes	8 (9.5%)	14 (16.9%)	22 (26.2%)
Adverse Events	1 (1.2%)	5 (6.0%)	10 (11.9%)
Withdrawal of Consent	1 (1.2%)	5 (6.0%)	9 (10.7%)
Lack of Efficacy	5 (6.0%)	1 (1.2%)	0
Lost to Follow up	0	2 (2.4%)	2 (2.4%)
Other	1 (1.2%)	1 (1.2%)	0
Non-Compliance	0	0	1 (1.2%)

Primary and Key Secondary Efficacy Endpoints at Week 12 Failed to Differentiate from Placebo



Bars represent 95% Confidence Intervals

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Overall Summary of Adverse Events (AE): More Treatment Emergent Adverse Events (TEAE) and Discontinuations Due to AEs with Increasing Dose

Most TEAEs were Mild or Moderate

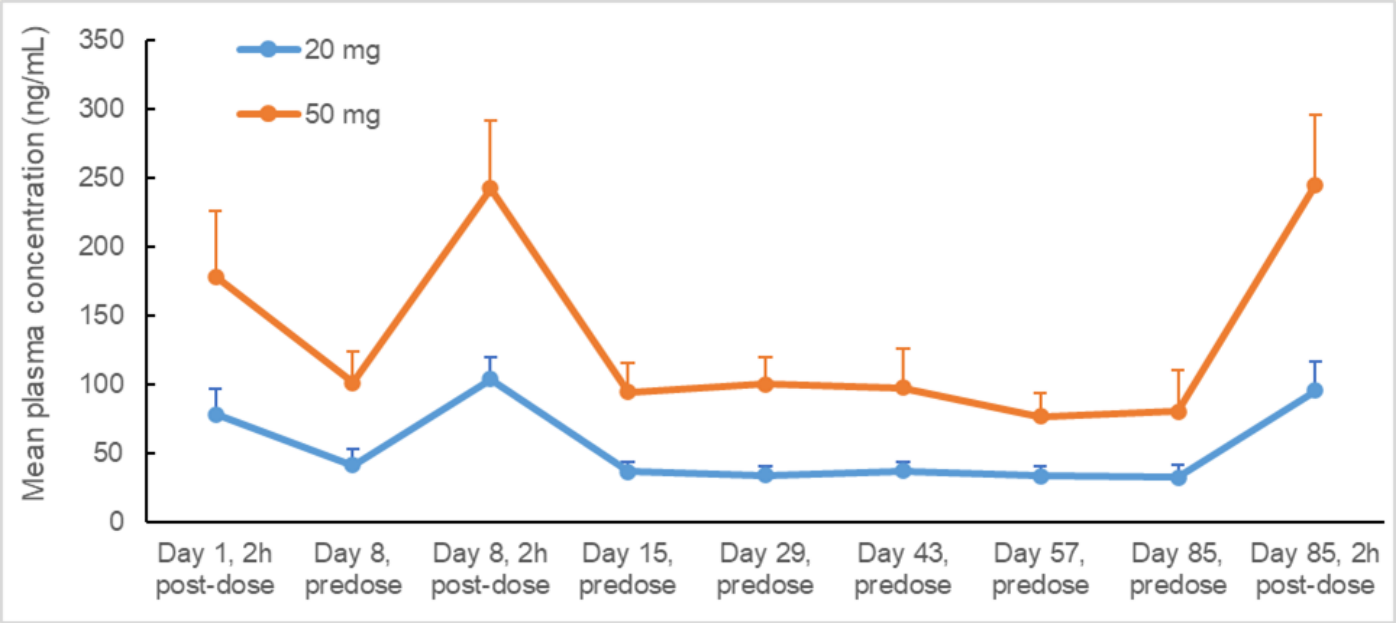
	Placebo (N=83)	ATI-450 20 mg (N=82)	ATI-450 50 mg (N=85)
Patients with any TEAE	24 (28.9%)	34 (41.5%)	44 (51.8%)
Patients with any Serious TEAE	1 (1.2%)	0	3 (3.5%)
Patients with any Mild TEAE	17 (20.5%)	21 (25.6%)	31 (36.5%)
Patients with any Moderate TEAE	10 (12.0%)	16 (19.5%)	21 (24.7%)
Patients with any Severe TEAE	1 (1.2%)	1 (1.2%)	3 (3.5%)
Patients with any Related TEAE	7 (8.4%)	14 (17.1%)	24 (28.2%)
Patients with any TEAE Leading to Discontinuation of Study Drug	1 (1.2%)	5 (6.1%)	10 (11.8%)
Patients with any Related TEAE Leading to Discontinuation of Study Drug	1 (1.2%)	4 (4.9%)	8 (9.4%)

TEAEs Occurring in ≥ 2 Patients in 50 mg arm by Preferred Term

Most common TEAEs on 50 mg are Nausea, Nasopharyngitis, CK increased, and Diarrhea

Preferred Term	Placebo BID	ATI-450 20 mg BID	ATI-450 50 mg BID
Nausea	1(1.2%)	2(2.4%)	4(4.7%)
Nasopharyngitis	3(3.6%)	2(2.4%)	3(3.5%)
Creatine phosphokinase increased	1(1.2%)	2(2.4%)	3(3.5%)
Diarrhea	1(1.2%)	1(1.2%)	3(3.5%)
Upper respiratory tract infection	1(1.2%)	5(6.1%)	2(2.4%)
Urinary tract infection	1(1.2%)	2(2.4%)	2(2.4%)
Abdominal pain upper	0	2(2.4%)	2(2.4%)
Arthralgia	1(1.2%)	1(1.2%)	2(2.4%)
Alanine aminotransferase increased	1(1.2%)	0	2(2.4%)
Aspartate aminotransferase increased	1(1.2%)	0	2(2.4%)
Headache	1(1.2%)	0	2(2.4%)
Rash	0	1(1.2%)	2(2.4%)
Vomiting	0	1(1.2%)	2(2.4%)
Acne	0	0	2(2.4%)
Aphthous ulcer	0	0	2(2.4%)
Bronchitis	0	0	2(2.4%)
Influenza	0	0	2(2.4%)
Palpitations	0	0	2(2.4%)
Tremor	0	0	2(2.4%)
Vertigo	0	0	2(2.4%)

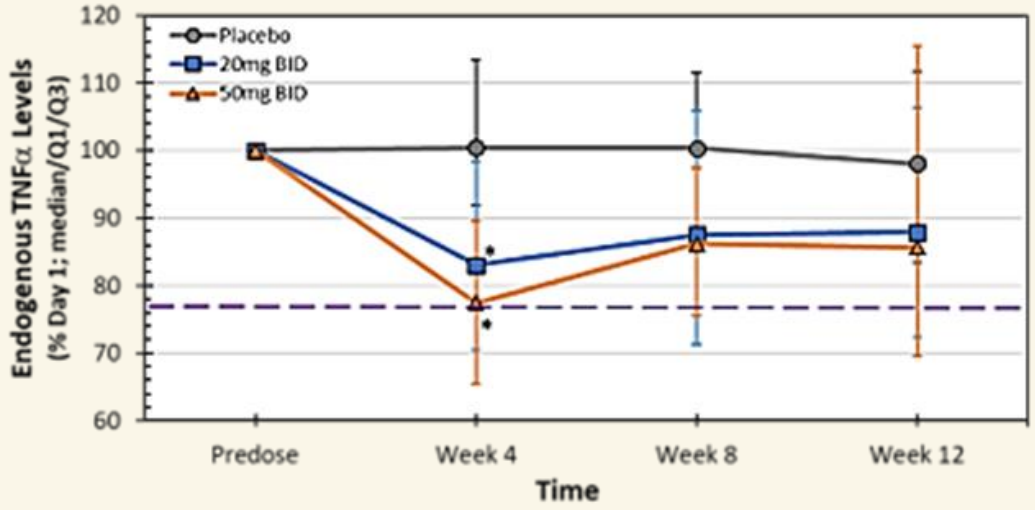
ATI-450 Plasma Concentrations



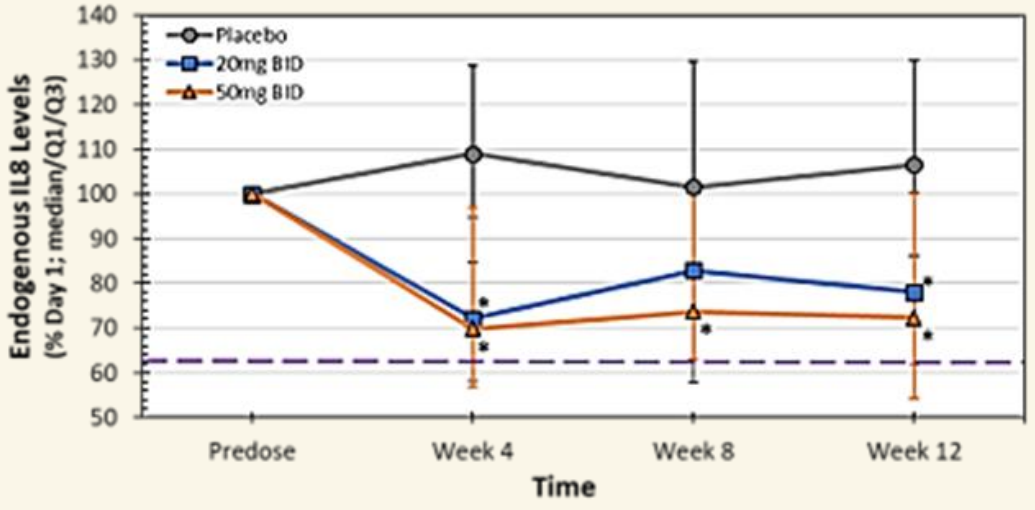
Mean ATI-450 Plasma Concentration 50 mg BID (ng/mL)	Co-Med	Day 1 2h postdose	Day 7/8 predose	Day 7/8 2h postdose	Day 84/85 predose	Day 84/85 2h postdose
Healthy Volunteers	-	178	88	200	-	-
RA-201 patients	MTX	226	164	-	125	293
HS-201 patients	-	148	102	208	104	242
RA-202 patients	MTX	179	101	242	80	245

Preliminary Exploratory Pharmacodynamic Analysis

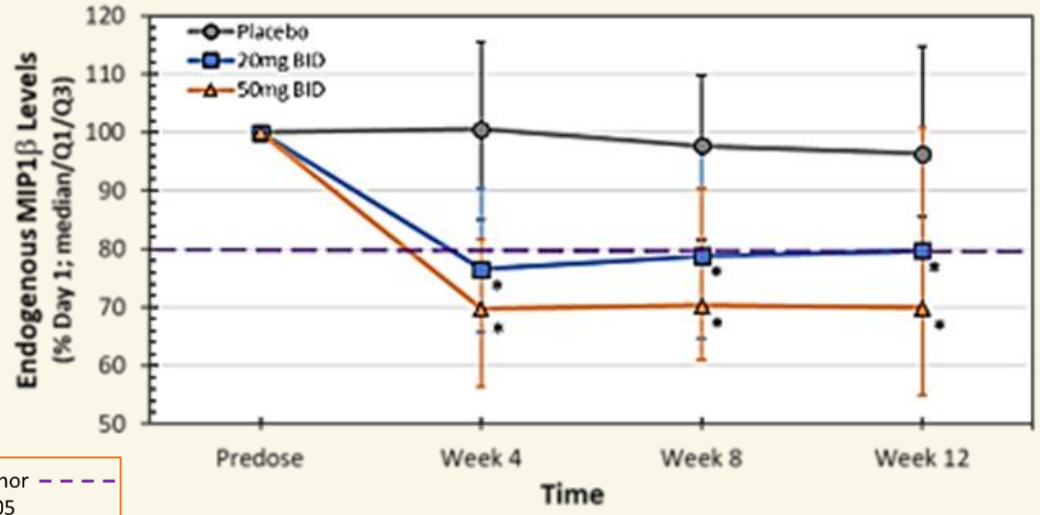
TNFα



IL8



MIP1β



Healthy Donor - - - -
(*) = p < 0.05

- Data calculated as percent Day 1 pre-dose by subject. Healthy donor levels expressed as percent of RA patient pre-dose levels
- An ATI-450 dependent, durable inhibition of the proinflammatory markers TNFα, IL8 and MIP1β was observed at both the 20 mg BID and 50 mg BID doses relative to placebo
- The IL1RA (anti-inflammatory cytokine) and IL6 were not inhibited at either dose (not shown)

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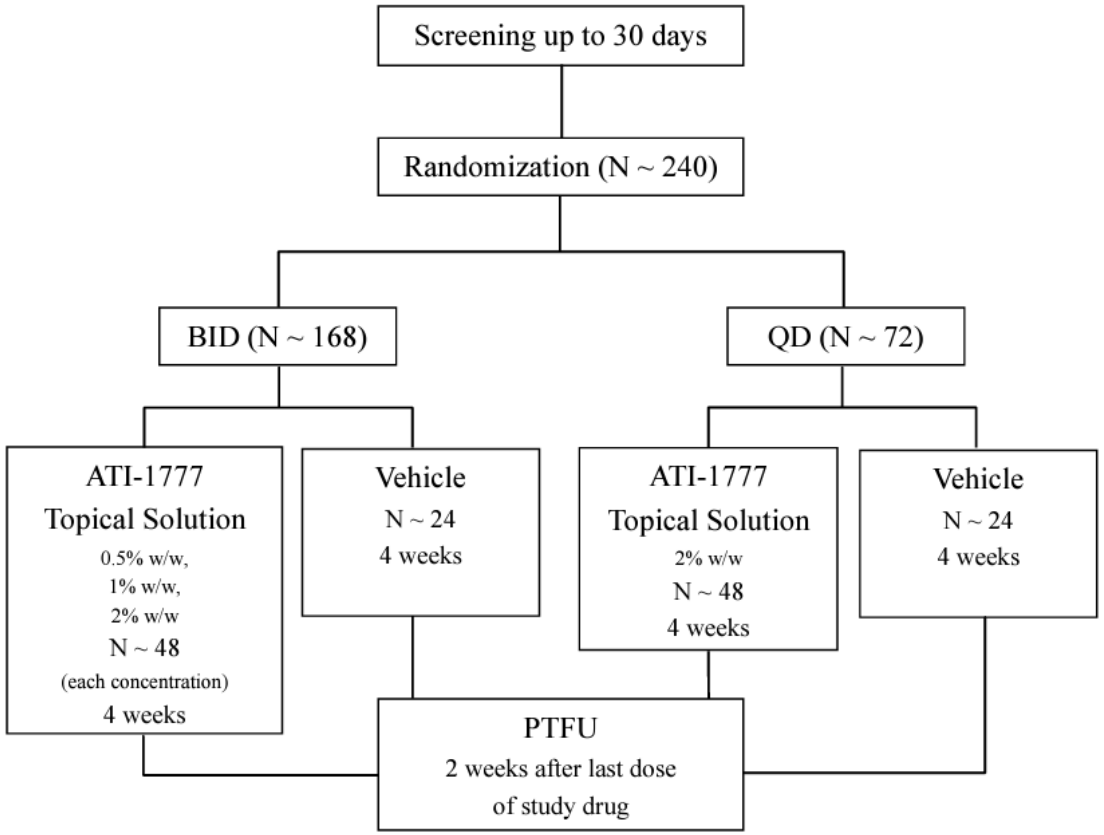
Summary of Results and Conclusions

- **Efficacy: ATI-450 20 mg BID and 50 mg BID did not differentiate from placebo in ACR20 and other measures**
  - Efficacy of ATI-450 20 mg BID, 50 mg BID and placebo were generally very similar at week 12 on all measures
  - Placebo response at higher end of the expected range
- **Safety: No meaningful safety findings**
  - More discontinuations due to AEs on ATI-450 (especially 50 mg BID) than placebo, although reasons are diverse
- **PK and PD**
  - PK dose proportional with exposure similar to HS-201 and healthy volunteer studies, while a little lower than RA-201
  - Proinflammatory PD biomarkers (TNFα, IL8 and MIP1β) performed as expected at both 20 and 50 mg BID relative to placebo while IL6 and the anti-inflammatory cytokine IL1RA were not inhibited at either dose

Phase 2b Trial of ATI-1777 in Atopic Dermatitis Results Expected Around Year End 2023

Phase 2b Multicenter, Randomized, Double-blind, Vehicle-controlled, Parallel-group Study to Determine the Safety, Tolerability, PK, and Efficacy of ATI-1777 in Patients 12-65 Years Old with Mild-Severe AD



Primary endpoint: % change from baseline to week 4 in EASI

Secondaries include:

- EASI-50, -75, -90
- % achieving IGA-TS
- % change BSA
- Change in vIGA
- PP-NRS
- PGIC
- POEM
- DLQI and CDLQI

Unique spray on solution

- ATI-1777: 0.5% BID, 1% BID, 2% BID, and 2% once daily
- Vehicle: a BID and once-daily arm

Drug Development Pipeline Fueled by the KINect® Platform Discovery Engine

Drug Candidate / Program	Target	Route of Administration	Indication	Development Phase
Immuno-Inflammatory Diseases				
ATI-1777	"Soft" JAK 1/3 inhibitor	Topical	Atopic dermatitis (mild to severe)	Phase 2b
ATI-2138	ITK/JAK3 inhibitor	Oral	T cell-mediated autoimmune diseases	Phase 2 Ready
Oncology				
ATI-2231	MK2 inhibitor	Oral	Metastatic breast cancer Pancreatic cancer	Phase 1a*

As of September 30, 2023, Aclaris had aggregate cash, cash equivalents and marketable securities of $187.0 million

* This is an investigator-initiated Phase 1a trial in patients with advanced solid tumor malignancies sponsored by Washington University.