

Pharmacokinetics, Safety, Pharmacodynamics, and Potency of ATN-249, a Novel Oral Plasma Kallikrein Inhibitor for Hereditary Angioedema

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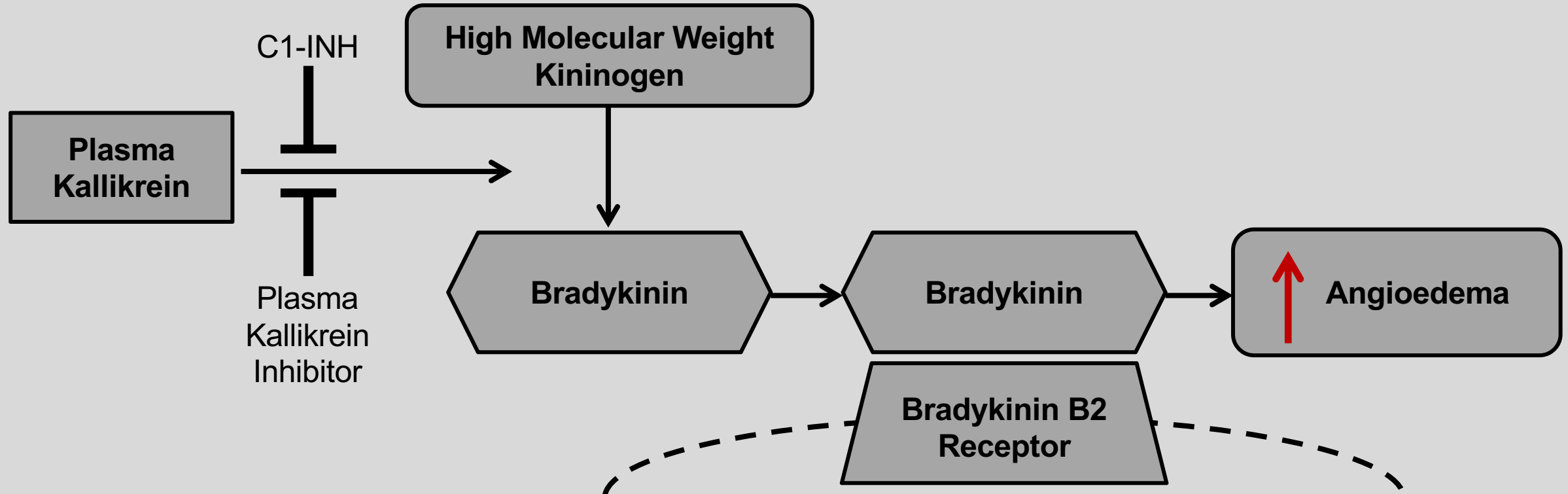
Disclosures

- ◆ CMO for Attune Pharmaceuticals, Inc.
- ◆ ATN-249 is an investigational agent which has not been approved by the FDA or the EMA

HAE Therapy

- ◆ Plasma derived C1-INH for prophylaxis – 2008
- ◆ Acute therapies within a year
- ◆ Lanadelumab and C1-INHsc recently approved
- ◆ Strong unmet need for effective, well tolerated, safe oral therapies with improved:
 - Quality of life
 - Convenience

ATN-249 – A New Oral Kallikrein Inhibitor



- ◆ Well characterized mechanism of action¹
- ◆ >1000 compounds synthesized
- ◆ ATN-249 selected on basis of chemical structure, selectivity and potency for plasma kallikrein and kallikrein inhibition
- ◆ Pre-clinical profile supported further development

Phase 1 Single Ascending Dose (SAD)¹

► Design

- ◆ 7 cohorts with 8 subjects randomized 6:2 with placebo
- ◆ 50, 100 (fasted/fed), 150, 200, 400, & 800 mg QD

► Results

- ◆ **Exposure:** Increased in a dose-dependent manner
- ◆ **PK:** Low to moderate between-subject variability
- ◆ **Safety:** Well tolerated:
 - No moderate/severe TEAEs
 - No drug-related TEAEs
 - No SAEs
 - No dose limiting toxicity

¹ Poster “Pharmacokinetics and Safety of ATN-249, a Novel Oral Plasma Kallikrein Inhibitor for Hereditary Angioedema” presented at WSAAI, January 20-24, 2019

Phase 1 Multiple Ascending Dose (MAD)

► Design

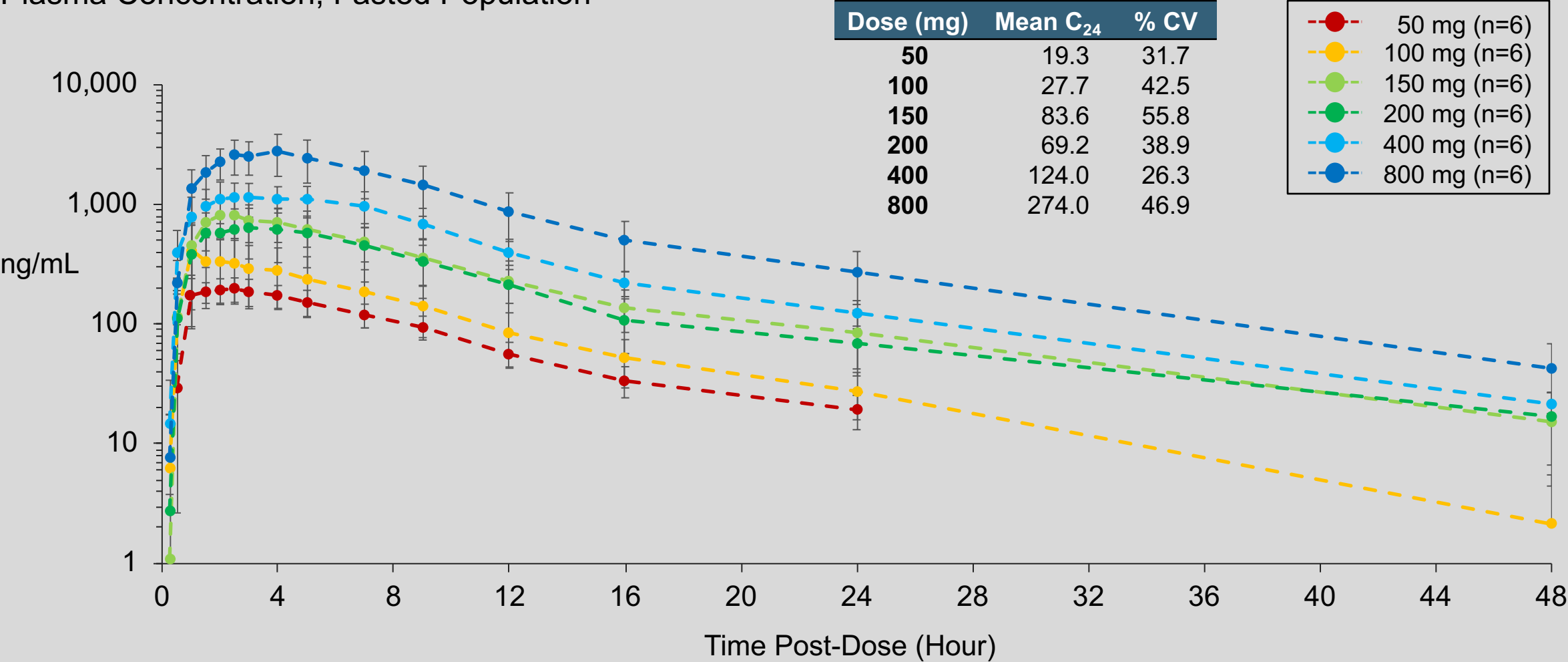
- ◆ 4 cohorts with 8 subjects randomized 6:2 with placebo
- ◆ 100, 200, 400 mg QD, & 300 mg BID
- ◆ 14 days of repeated dosing

► Results

- ◆ **PK:** Predictable and dose-linear with low to moderate between-subject variability
- ◆ **Safety:**
 - Well-tolerated
 - No drug related TEAEs
- ◆ **PD:** Trough levels well above the therapeutically relevant concentrations needed for inhibition

Single Ascending Dose PK

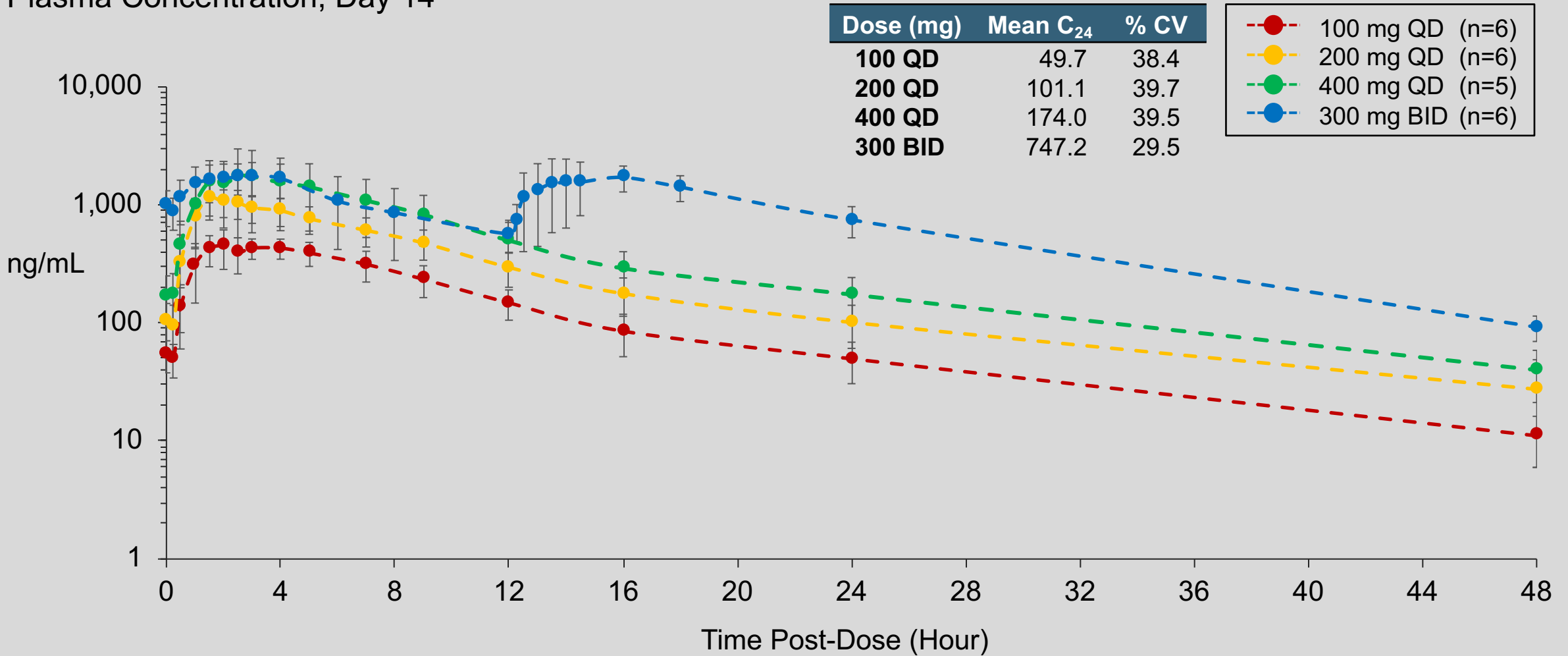
Plasma Concentration, Fasted Population



Exposure increased in a dose-dependent manner

Multiple Ascending Dose PK

Plasma Concentration, Day 14



Exposure increased in a dose-dependent manner

Multiple Ascending Dose PK Parameters

Day 14

Parameter Mean (% CV)	Dose (mg)			
	100 QD	200 QD	400 QD	300 BID
AUC_{tau} (ng*hr/mL)	4592 (26.9)	9749 (27.2)	16390 (47.8)	28740 (26.4)
C_{avg} (ng/mL)	191 (26.9)	406 (27.2)	683 (47.8)	1198 (26.4)
C_{max} (ng/mL)	496 (22.7)	1202 (26.1)	2010 (60.5)	2040 (28.6)
C_{min} (ng/mL)	47 (36.0)	92 (44.5)	153 (45.1)	527 (28.2)
T_{max} (Hours)	2.4 (35.6)	2.2 (49.9)	1.9 (43.2)	1.9 (43.2)
T_{1/2} (Hours)	10.9 (8.1)	10.5 (30.3)	11.7 (20.4)	7.7 (7.6)

- ◆ AUC, C_{avg}, C_{max}, and C_{min} increased proportionally with dose
- ◆ T_{max} and T_{1/2} consistent across dose cohorts

Multiple Ascending Dose Safety Summary

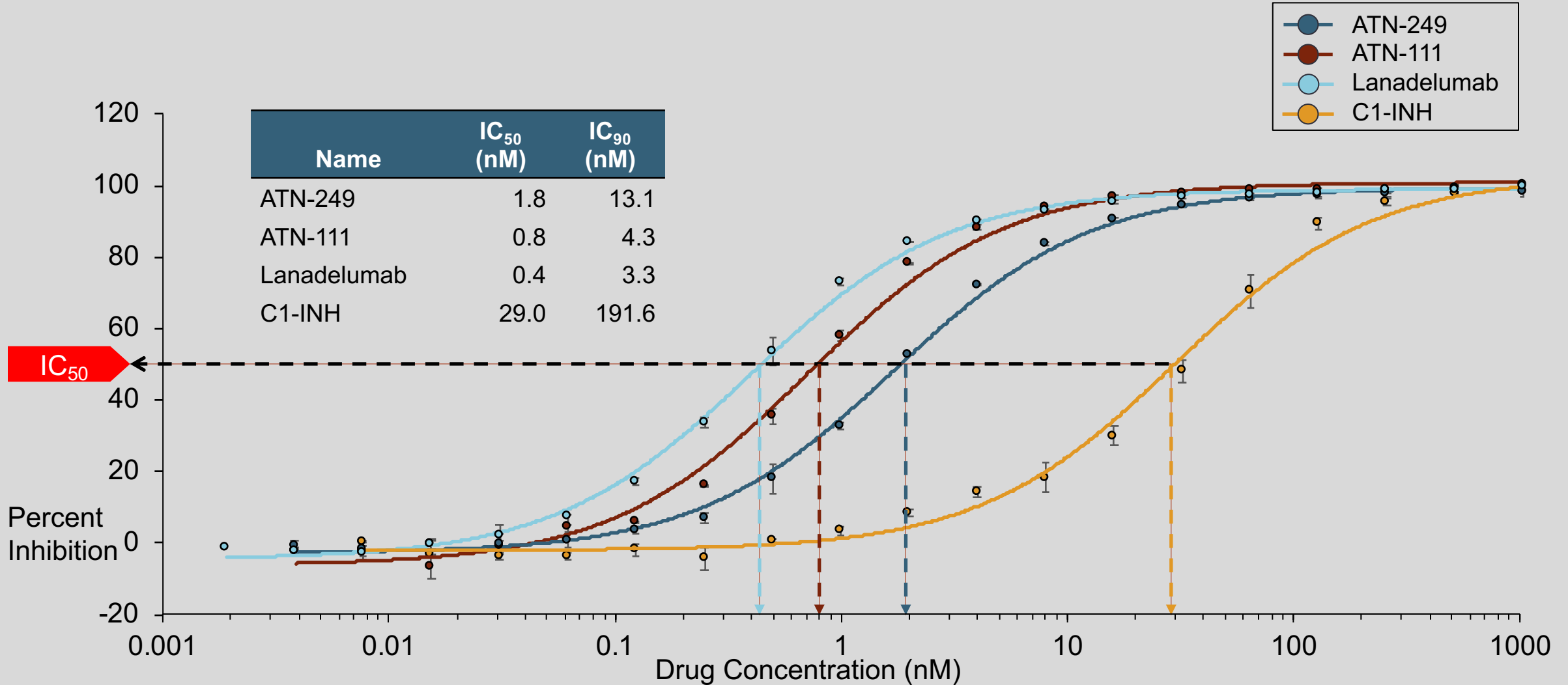
- ◆ 113 TEAEs
 - None related to investigational drug
 - 86 drug arm & 27 placebo arm
 - Majority were mild: 106 mild & 7 moderate
- ◆ 1 SAE – Not related to investigational drug
 - Asymptomatic cardiac arrhythmia
- ◆ No clinically significant laboratory or EKG abnormalities
- ◆ One subject withdrew on Day 15 as requested due to personal issues

TEAEs – Instance & Type >10% of Patients

Adverse Event	ATN-249 (N=24)	Instance	Placebo (N=8)	Instance
	% (n)	n	% n	n
Total TEAEs	95.8 (23)	86	87.5 (7)	27
By type (>10%):				
Gastrointestinal disorders	50.0 (12)	22	37.5 (3)	5
General disorders & cannulation site conditions	41.7 (10)	12	50.5 (4)	6
Nervous system disorders	41.7 (10)	21	37.5 (3)	5
Skin & subcutaneous tissue disorders	20.8 (5)	7	0.0 (0)	0
Cardiac disorders	16.7 (4)	4	12.5 (1)	1
Infections & infestations	16.7 (4)	5	37.5 (3)	4
Injury, poisoning & procedural complications	16.7 (4)	4	12.5 (1)	1
Musculoskeletal & connective tissue disorders	16.7 (4)	4	25.0 (2)	3
Respiratory, thoracic & mediastinal disorders	12.5 (3)	1	12.5 (1)	1

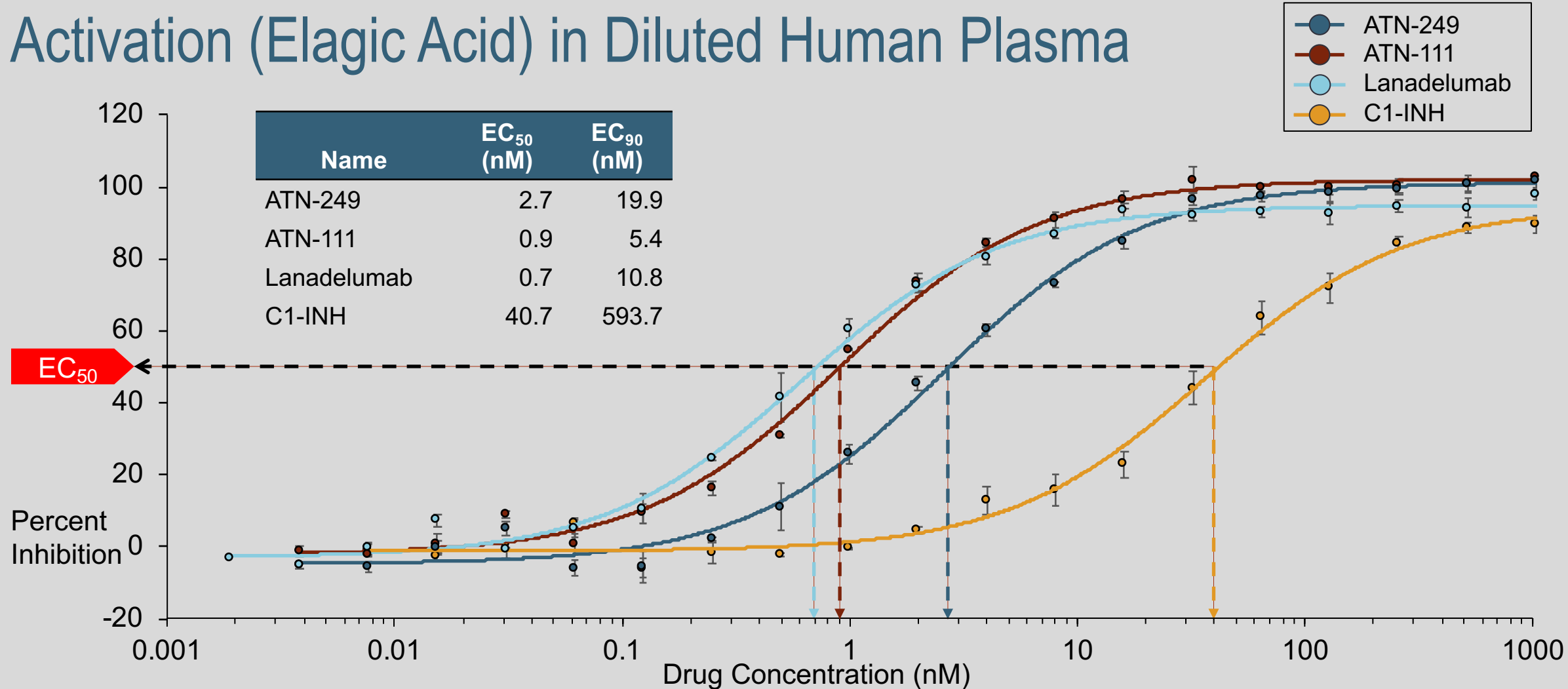
- ◆ Comparable safety profile vs. placebo
- ◆ TEAEs were self limited and not drug related

Biochemical Inhibition of Plasma Kallikrein



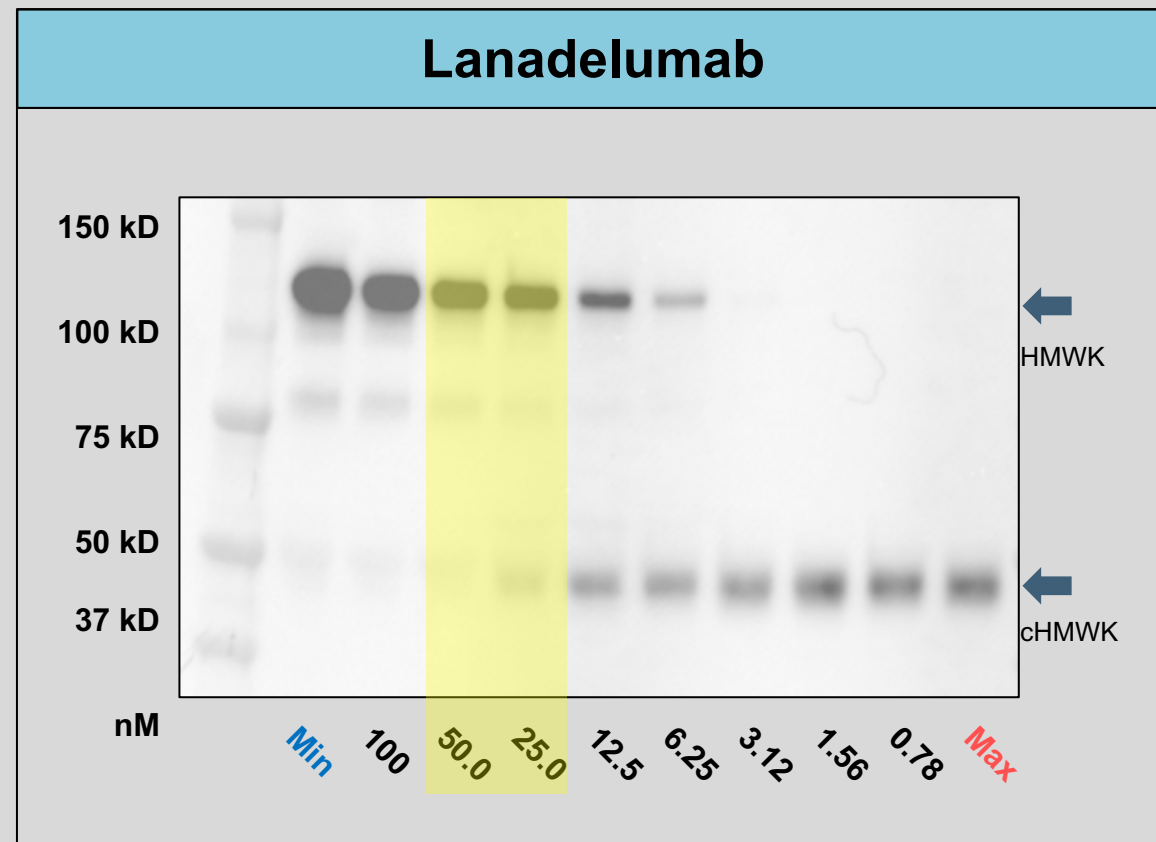
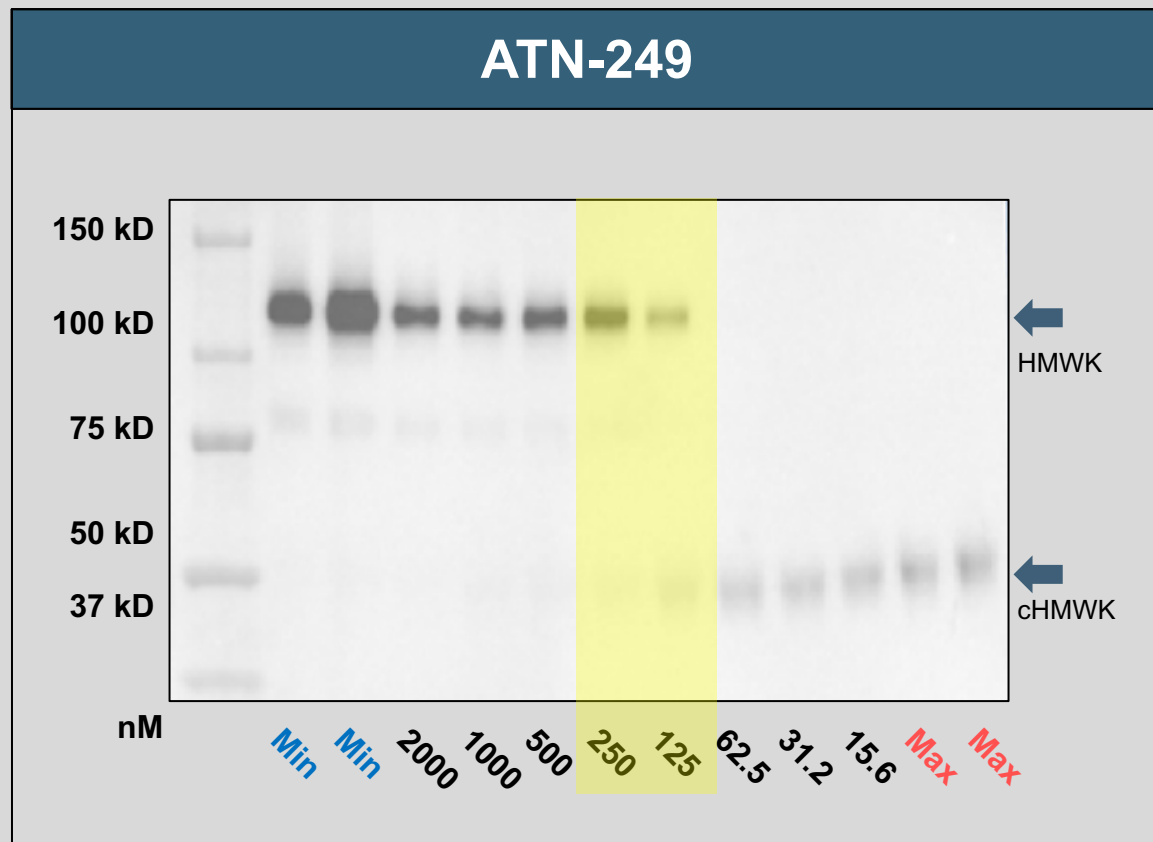
- ◆ 16-fold higher potency vs. C1-INH
- ◆ 4-fold lower potency vs. lanadelumab

Inhibition of Plasma Kallikrein via Contact Assay Activation (Elagic Acid) in Diluted Human Plasma



- ◆ 15-fold higher potency vs. C1-INH
- ◆ 4-fold lower potency vs. lanadelumab

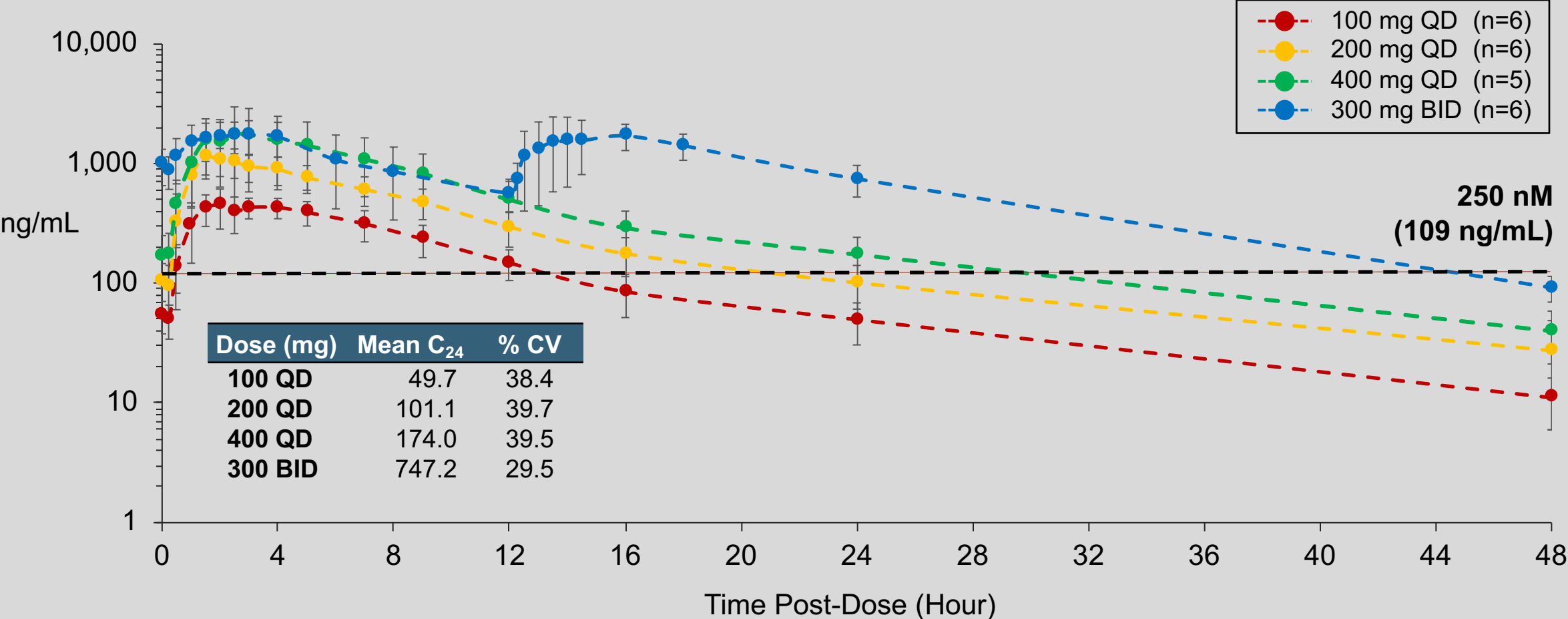
Western Blot Analysis of Cleaved HMWK¹ in Healthy Volunteers' Whole Plasma Activated by DXS



- ◆ ATN-249: >80% inhibition of cleaved kininogen at 125-250 nM
- ◆ Lanadelumab: >80% inhibition at 25-50 nM

Multiple Ascending Dose PK

Plasma Concentration, Day 14



Dosing as low as 100 mg BID is expected to achieve the trough concentration needed for inhibition

Conclusions and Discussion

- ◆ MAD:
 - **PK:** Predictable and dose-linear with low to moderate between-subject variability
 - **Safety:** Well-tolerated and no drug related TEAEs
 - **PD:** Trough levels well above the therapeutically relevant concentrations
- ◆ In vitro inhibition comparable to lanadelumab
- ◆ Potentially a best-in-class safe, oral plasma kallikrein inhibitor for prophylactic treatment of HAE
- ◆ Phase 2 study planned

Thank You