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

IRA KALFUS, MD
Attune Pharmaceuticals, Inc.
New York City, NY, USA

[1]Elliot Offman, PhD; [2]Andrew McDonald, PhD
[1]Certara Strategic Consulting, Toronto, ON, Canada
[2]Attune Pharmaceuticals, Inc., New York City, NY, USA

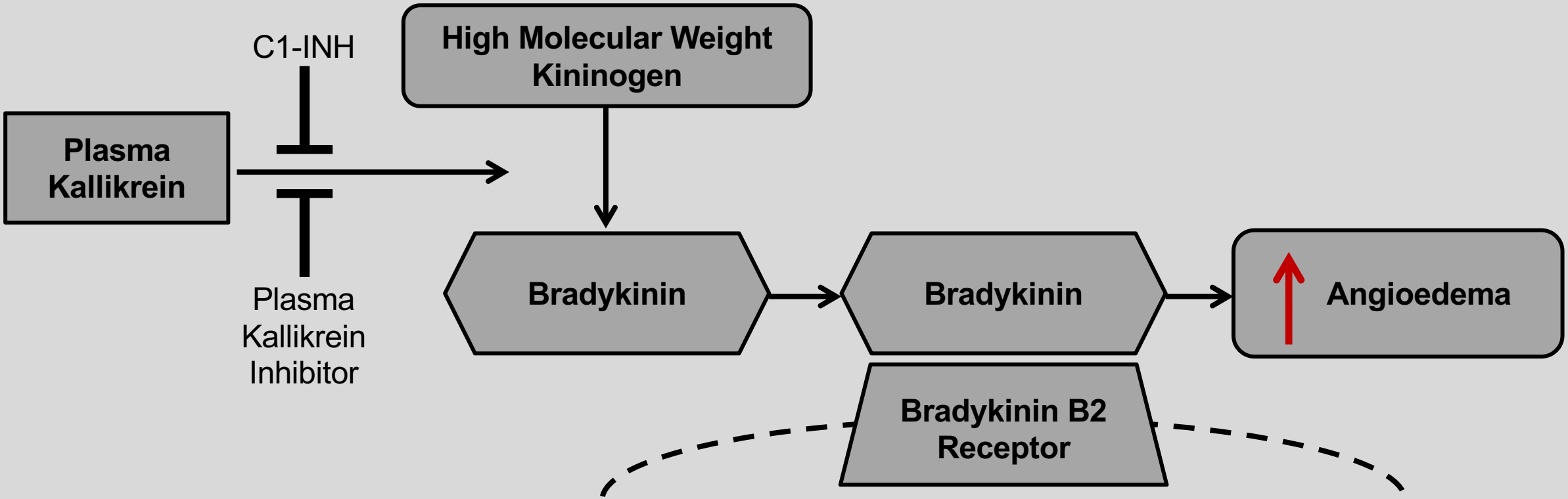
Disclosures

- 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 action[1]
- >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

1 Adapted from Ameratunga R, et al. Front Immunol. 2016

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

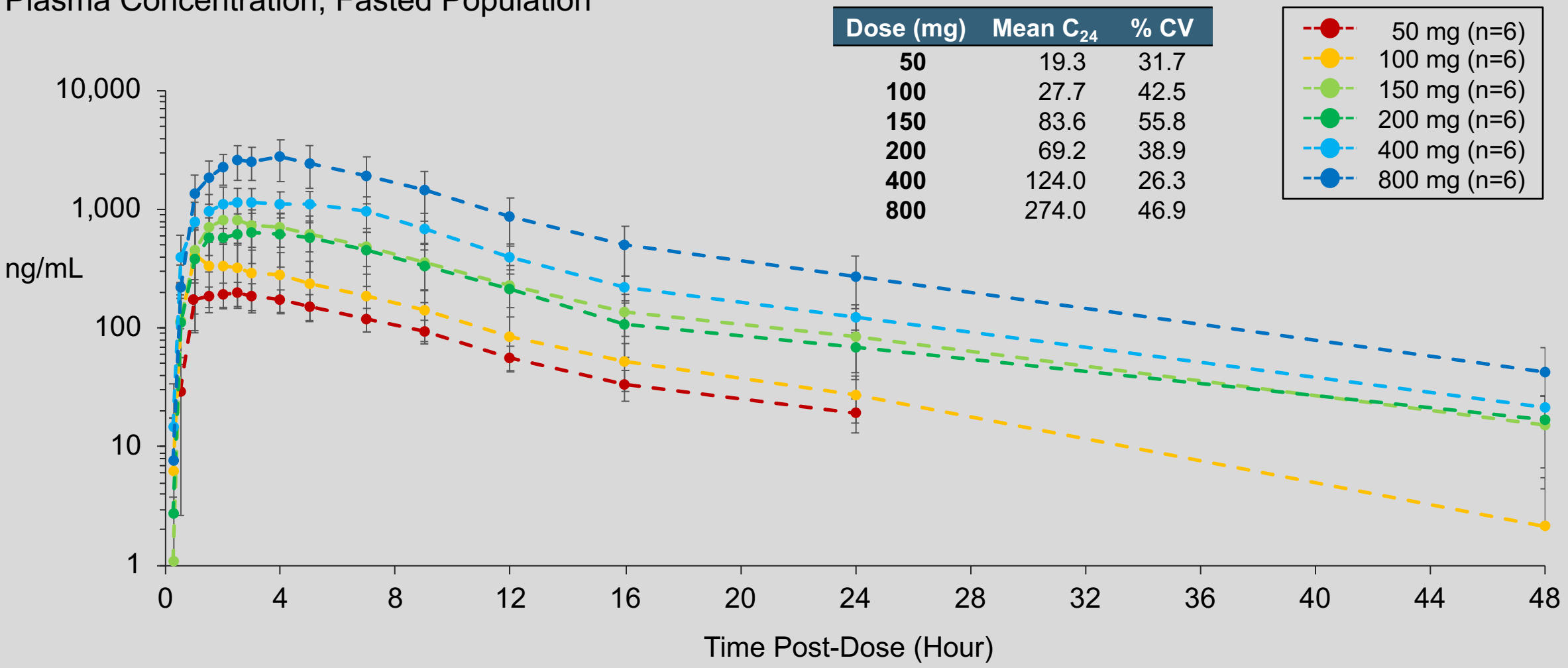
Results

- **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

Dose (mg)	Mean C_{24}	% CV
50	19.3	31.7
100	27.7	42.5
150	83.6	55.8
200	69.2	38.9
400	124.0	26.3
800	274.0	46.9

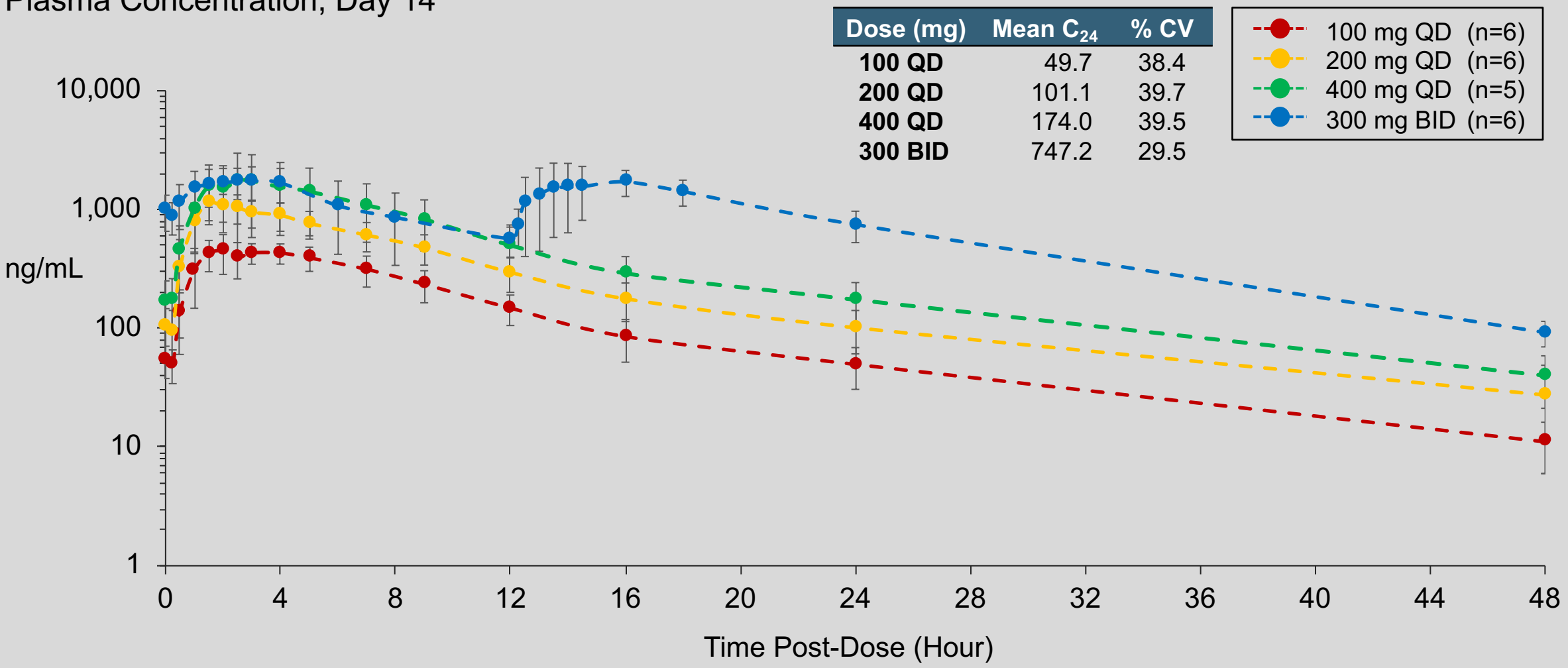


Exposure increased in a dose-dependent manner

Multiple Ascending Dose PK

Plasma Concentration, Day 14

Dose (mg)	Mean C_{24}	% CV
100 QD	49.7	38.4
200 QD	101.1	39.7
400 QD	174.0	39.5
300 BID	747.2	29.5



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 cardia arrhythmia

- No clinically significant laboratory or EKG abnormalities

- One subject withdrew on Day 15 as requested due to personal issues

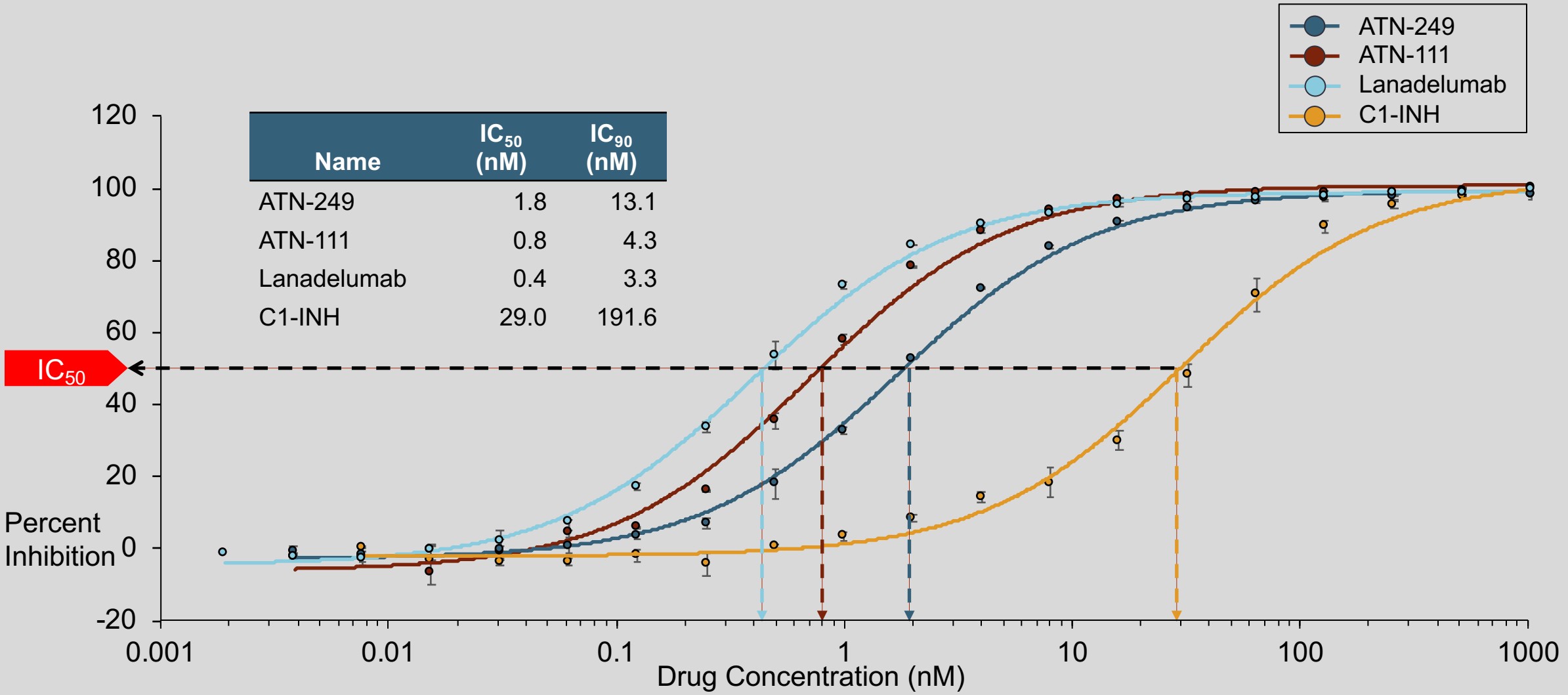
TEAEs – Instance & Type >10% of Patients

Adverse Event	ATN-249 (N=24) % (n)	Instance n	Placebo (N=8) % n	Instance 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

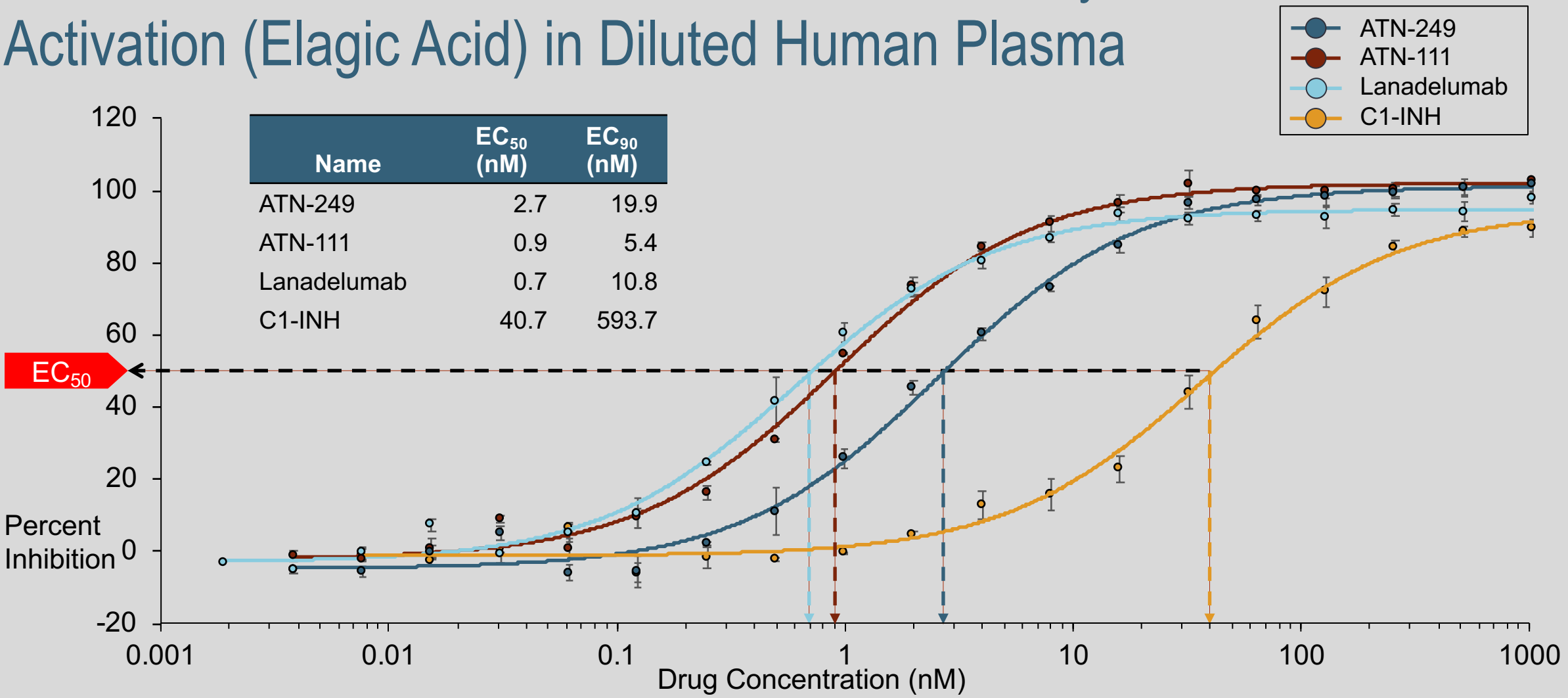
Name	IC_{50} (nM)	IC_{90} (nM)
ATN-249	1.8	13.1
ATN-111	0.8	4.3
Lanadelumab	0.4	3.3
C1-INH	29.0	191.6



- 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

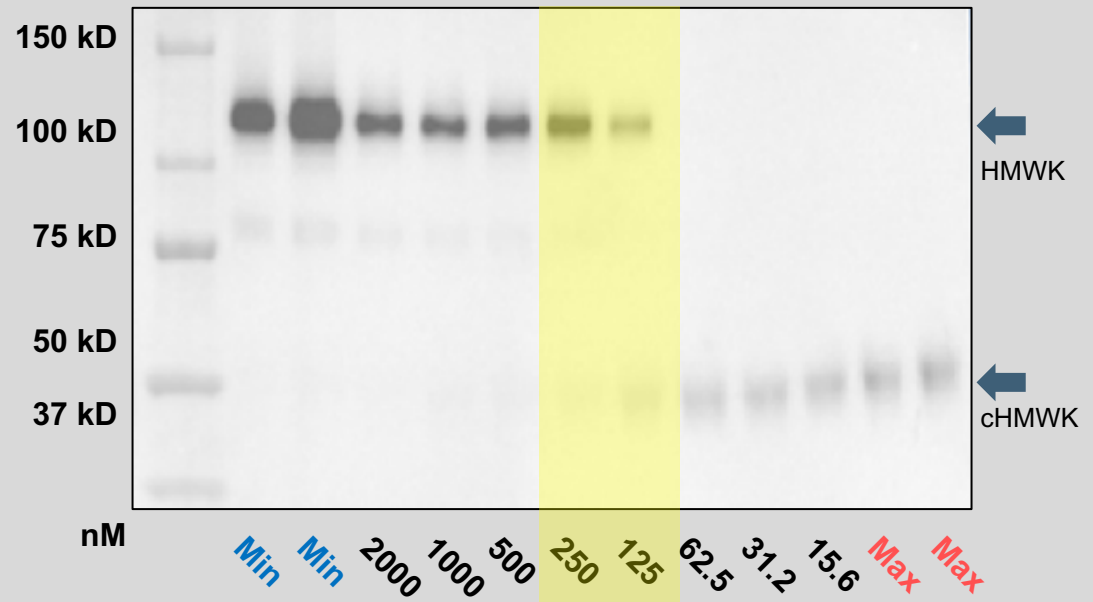
Name	EC_{50} (nM)	EC_{90} (nM)
ATN-249	2.7	19.9
ATN-111	0.9	5.4
Lanadelumab	0.7	10.8
C1-INH	40.7	593.7



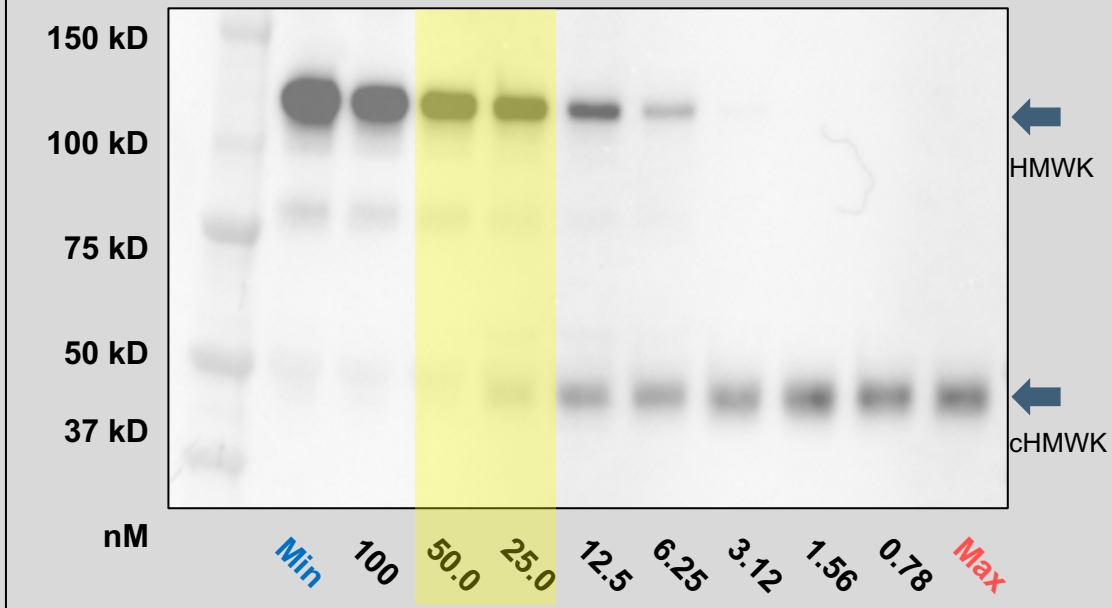
- 15-fold higher potency vs. C1-INH
- 4-fold lower potency vs. lanadelumab

Western Blot Analysis of Cleaved HMWK[1] in Healthy Volunteers' Whole Plasma Activated by DXS

ATN-249



Lanadelumab

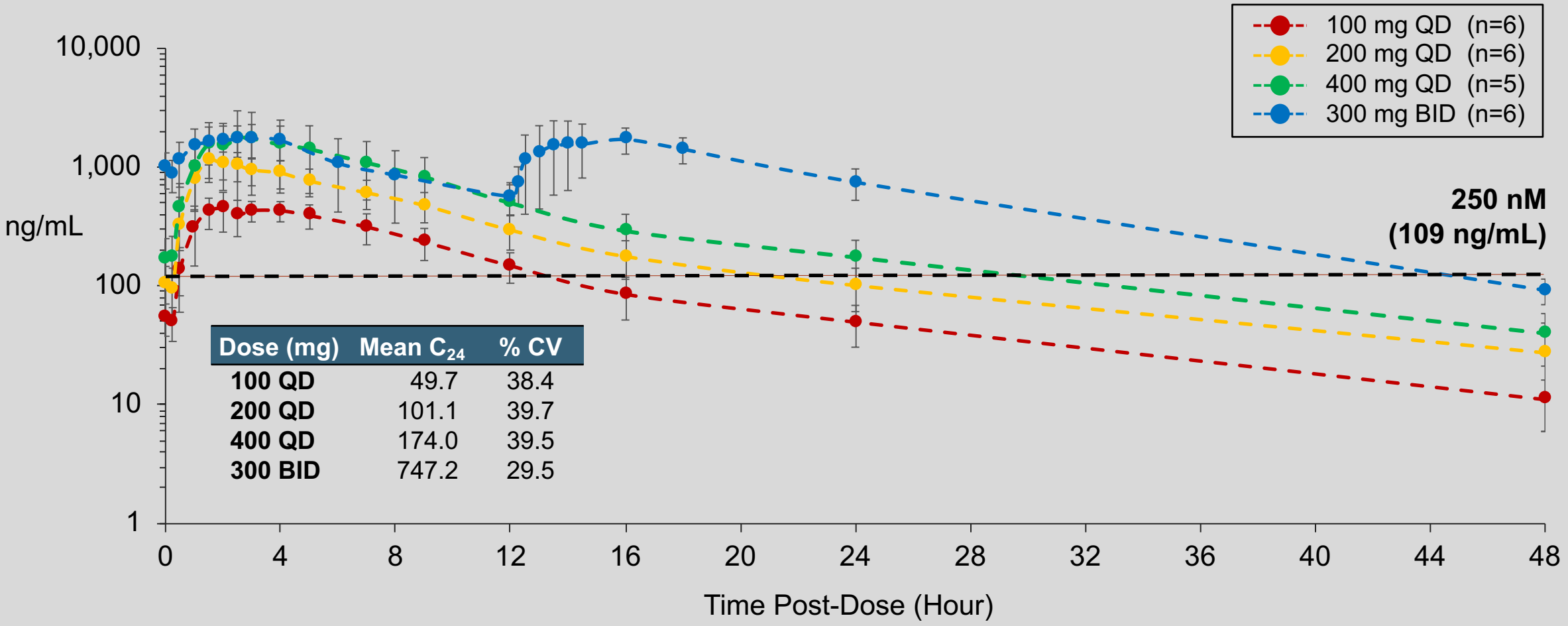


- ATN-249: >80% inhibition of cleaved kininogen at 125-250 nM
- Lanadelumab: >80% inhibition at 25-50 nM

1 High-molecular-weight kininogen

Multiple Ascending Dose PK

Plasma Concentration, Day 14



Dose (mg)	Mean C_{24}	% CV
100 QD	49.7	38.4
200 QD	101.1	39.7
400 QD	174.0	39.5
300 BID	747.2	29.5

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