Safety Study of ATN-249, A New Oral Kallikrein Inhibitor for Hereditary Angioedema

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Disclosures

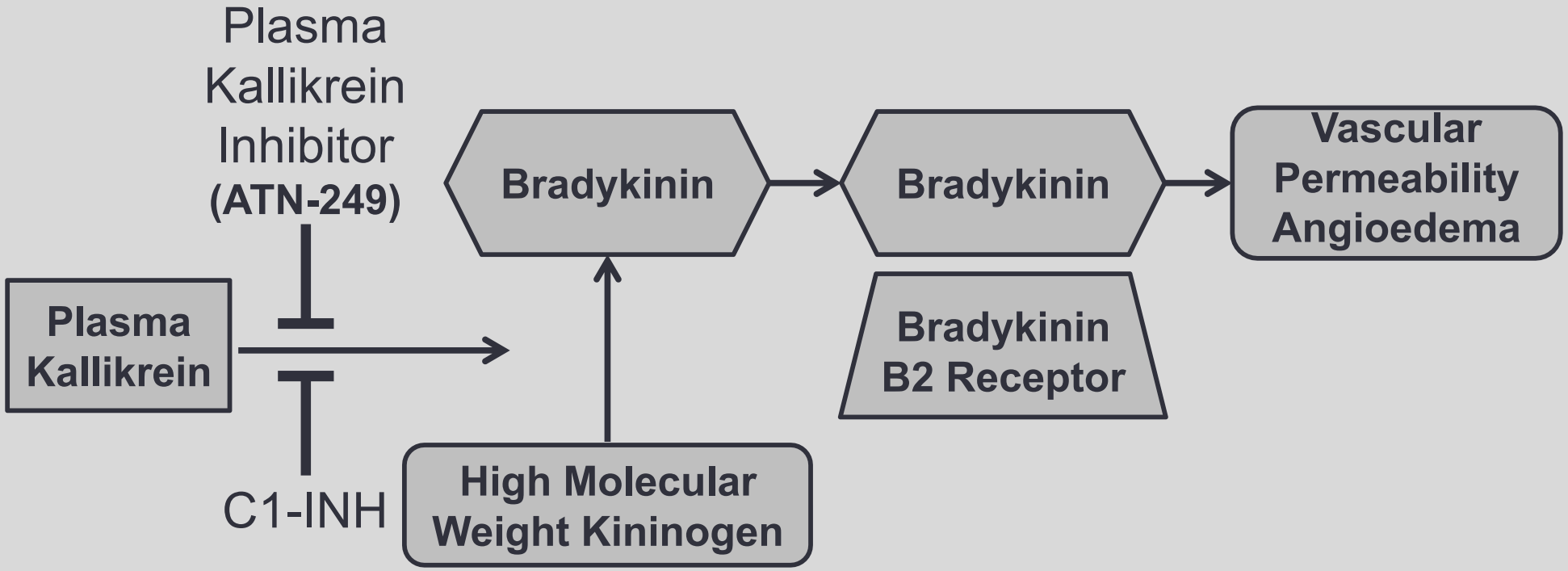
- CMO for Attune Pharmaceuticals, LLC
- ATN-249 is an investigational agent which has not been approved by the FDA or the EMA

HAE Therapy

- Plasma derived C1INH for prophylaxis – 2008
- Acute therapies within a year
- New IV and SC prophylactic therapies coming
- Strong unmet need for effective, well tolerated, safe oral therapies with improved:[1]
  - Patient quality life
  - Convenience
  - Prophylactic Efficacy

1 Shire 2014 and 2015 HAE Patient and Physician Surveys

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 for plasma kallikrein and kallikrein inhibition

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

Main Objectives of Preclinical Studies of ATN-249

Potency

- Evaluate potency of ATN-249 compared to C1INH via inhibition of plasma kallikrein

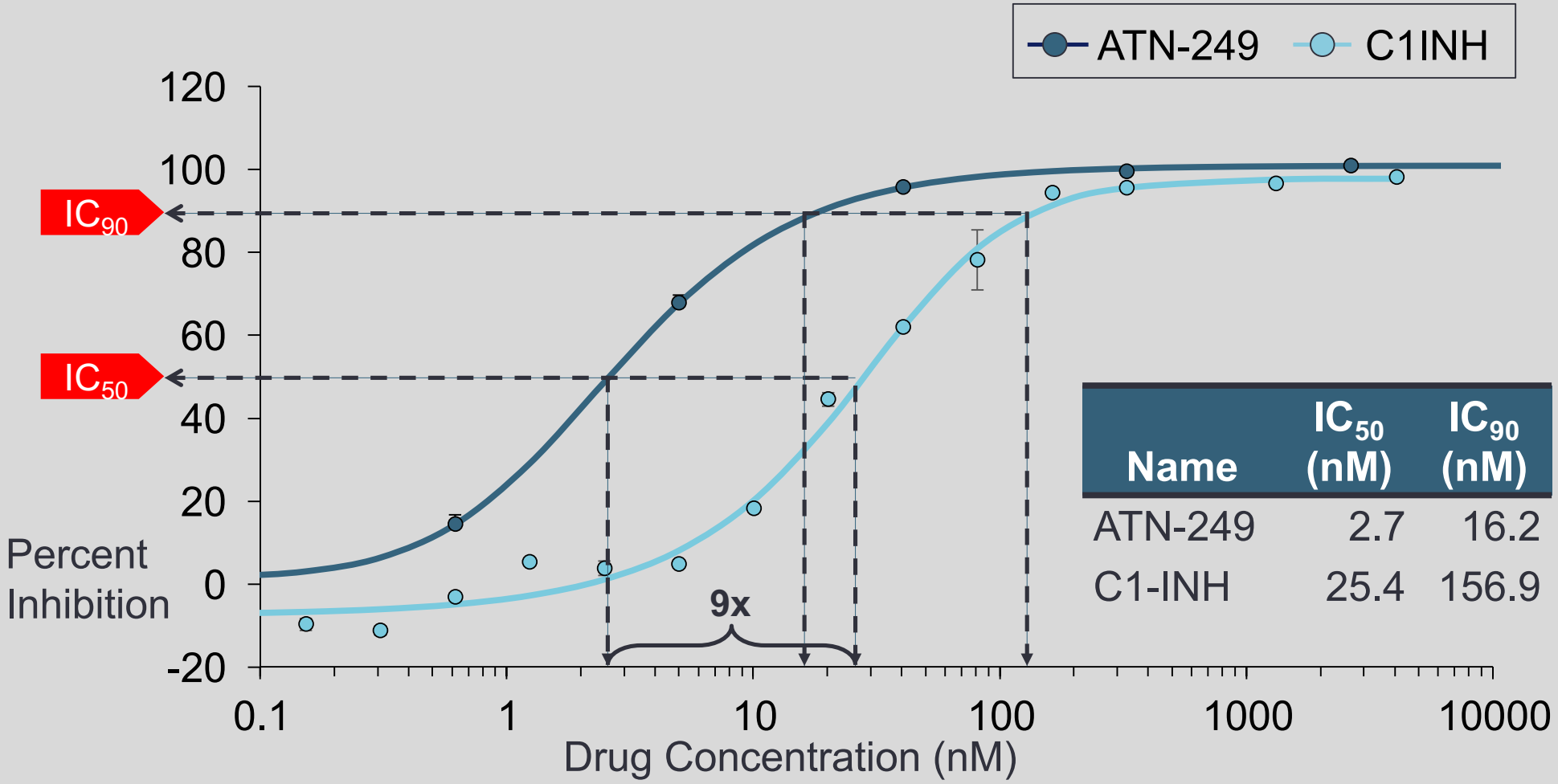
Selectivity

- Evaluate selectivity of ATN-249 on biochemical inhibition of plasma kallikrein relative to other closely related serine proteases

Safety

- Evaluate ATN-249's pharmacokinetics, general toxicity, safety pharmacology, and genotoxicity profiles

Biochemical Inhibition of Plasma Kallikrein

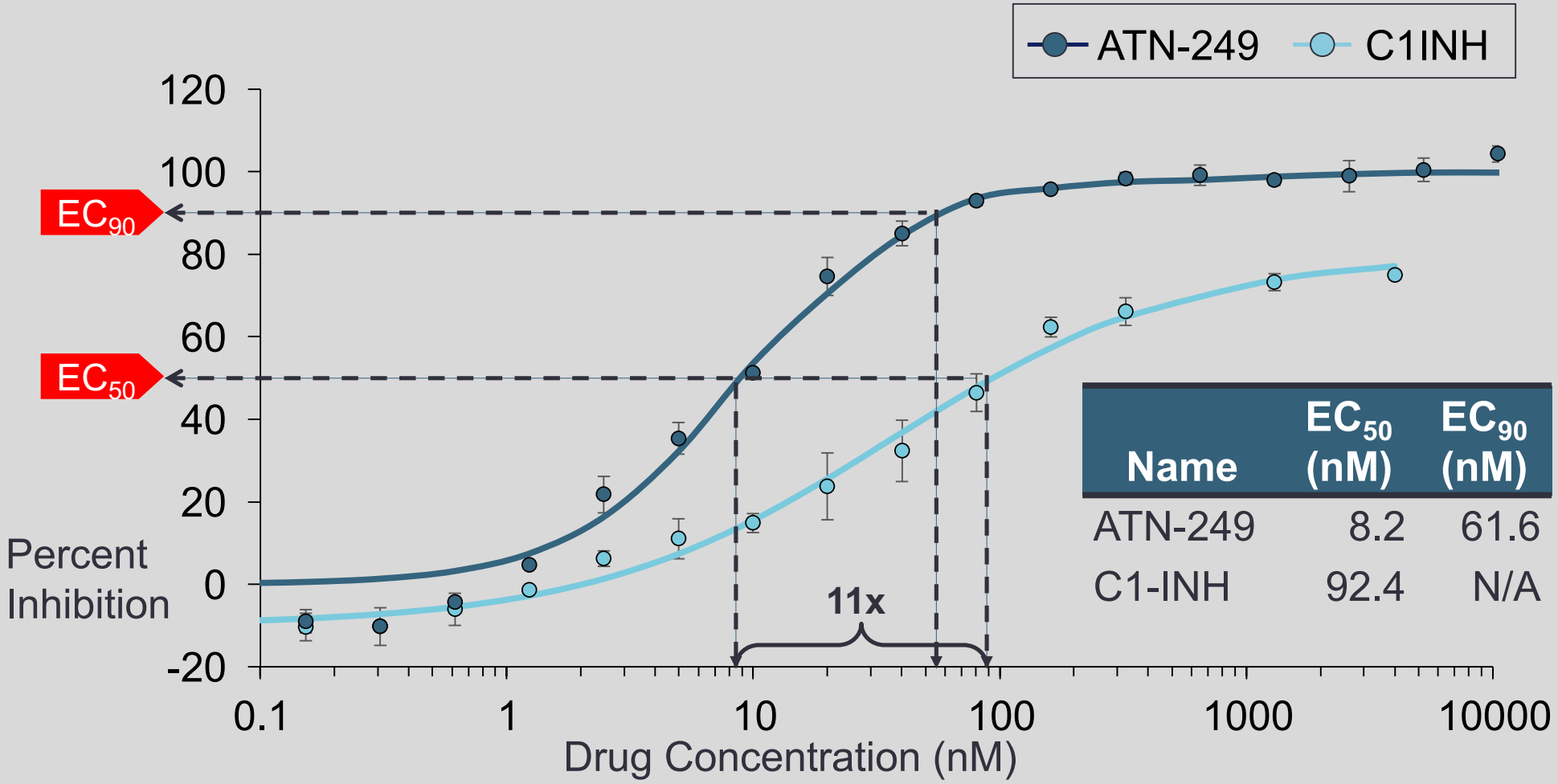


Name	IC_{50} (nM)	IC_{90} (nM)
ATN-249	2.7	16.2
C1-INH	25.4	156.9

ATN-249 was 9-fold more potent than C1-INH at inhibiting plasma kallikrein in biochemical inhibition

SOURCE: ATN-249 ET-1 Potency Report

Inhibition of Plasma Kallikrein via Contact Activation Assay in Human Plasma



Name	EC_{50} (nM)	EC_{90} (nM)
ATN-249	8.2	61.6
C1-INH	92.4	N/A

ATN-249 was 11-fold more potent than C1-INH at inhibiting plasma kallikrein in contact activation assay

SOURCE: ATN-249 ET-2 Potency Report

Selectivity – ATN-249 Biochemical Inhibition of Plasma Kallikrein vs Other Serine Proteases

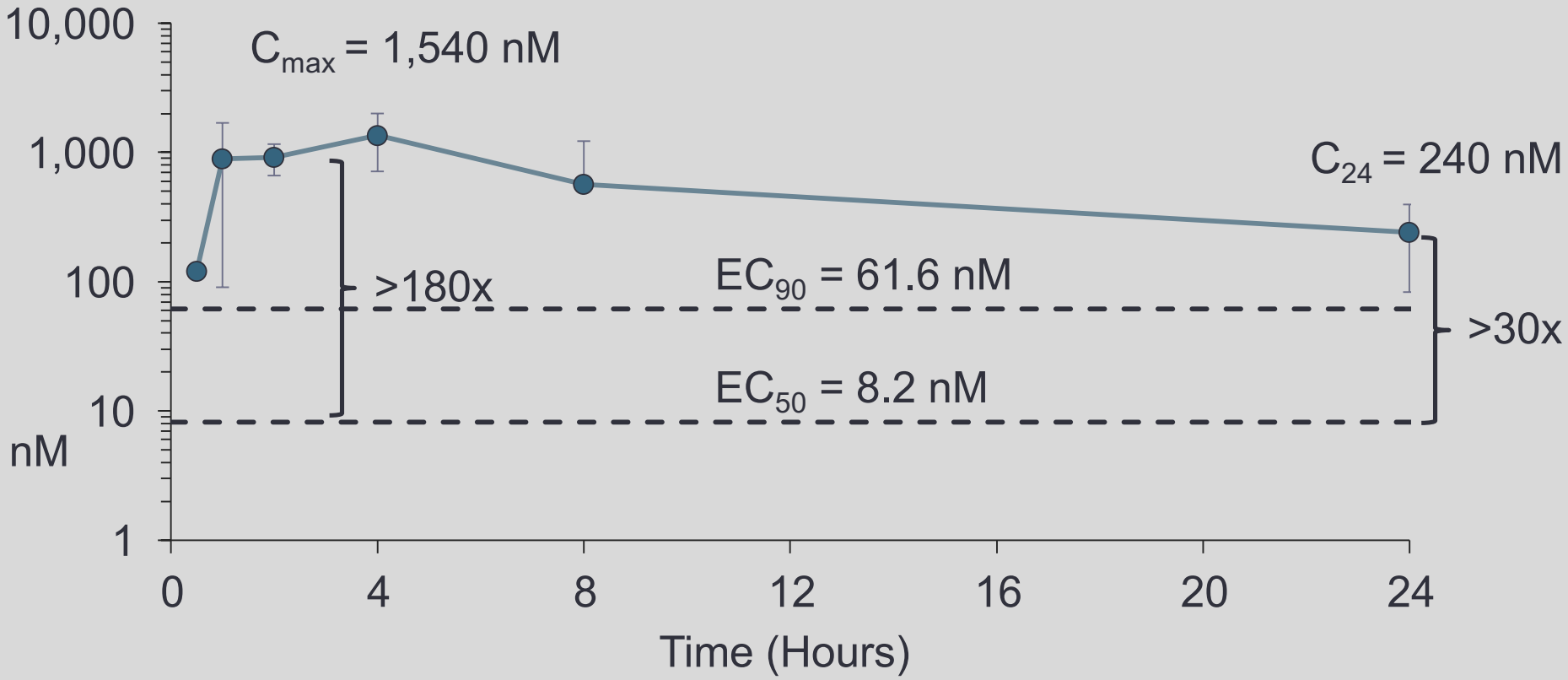
Serine Protease	IC_{50} (nM)
Plasma Kallikrein	2.7
Plasmin	>6,000
Tissue Kallikrein 5	>100,000
Tissue Kallikrein 7	>2,000
Tissue Kallikrein 14	>70,000
Factor Xa	>50,000
Factor VIIa	>100,000
Thrombin	>100,000
Tissue Plasminogen Activator (tPA)	>100,000

ATN-249 demonstrated >2000-fold selectivity at plasma kallikrein inhibition vs. other related serine proteases

SOURCE: ATN-249 Selectivity Reports

Exposure – Single Dose in Monkey

Mean±SD Plasma Concentration After Single Oral Dosing of ATN-249 at 15 mg/kg



ATN-249 provided C_{max} exposure >180x and 24hr exposure (C_{24}) 30-fold >EC_{50}

SOURCE: ATN-249 Single Dose Monkey PK Report

Cytochrome P450 Inhibition – Drug Concentration Required for Cytochrome P450 (CYP) Inhibition

CYP Enzymes	Control (µM)	ATN-249 (µM)
1A2	0.004	>50.0
2B6	0.171	>50.0
2C8	0.042	22.8
2C9	0.683	35.4
2C19	0.108	19.9
2D6	0.050	21.5
3A4-M	0.011	9.6
3A4-T	0.012	6.2

ATN-249 does not significantly inhibit P450 enzymes

SOURCE: ATN-249 CYP Inhibition (Direct) Report

Metabolism and Pharmacokinetics Results of Single Oral Dosing of ATN-249

Study	Result
Metabolism[1]	• Intact rats: 99% recovered in feces • Bile duct cannulated (BDC) rats: – 52% recovered in feces – 39% recovered in bile
Pharmacokinetics	• >50% bioavailability in rats & dogs • ~40% bioavailability in monkeys

After single oral administration, ATN-249 demonstrated:

- Good bioavailability in all species
- Comprehensive recovery of radiolabeled ATN-249

1 Metabolism study was conducted with radiolabeled [^{14}C] ATN-249

SOURCE: ATN-249 Rat C14 Mass Balance Reports; ATN-249 Single Dose Rat and Monkey Bioavailability Reports

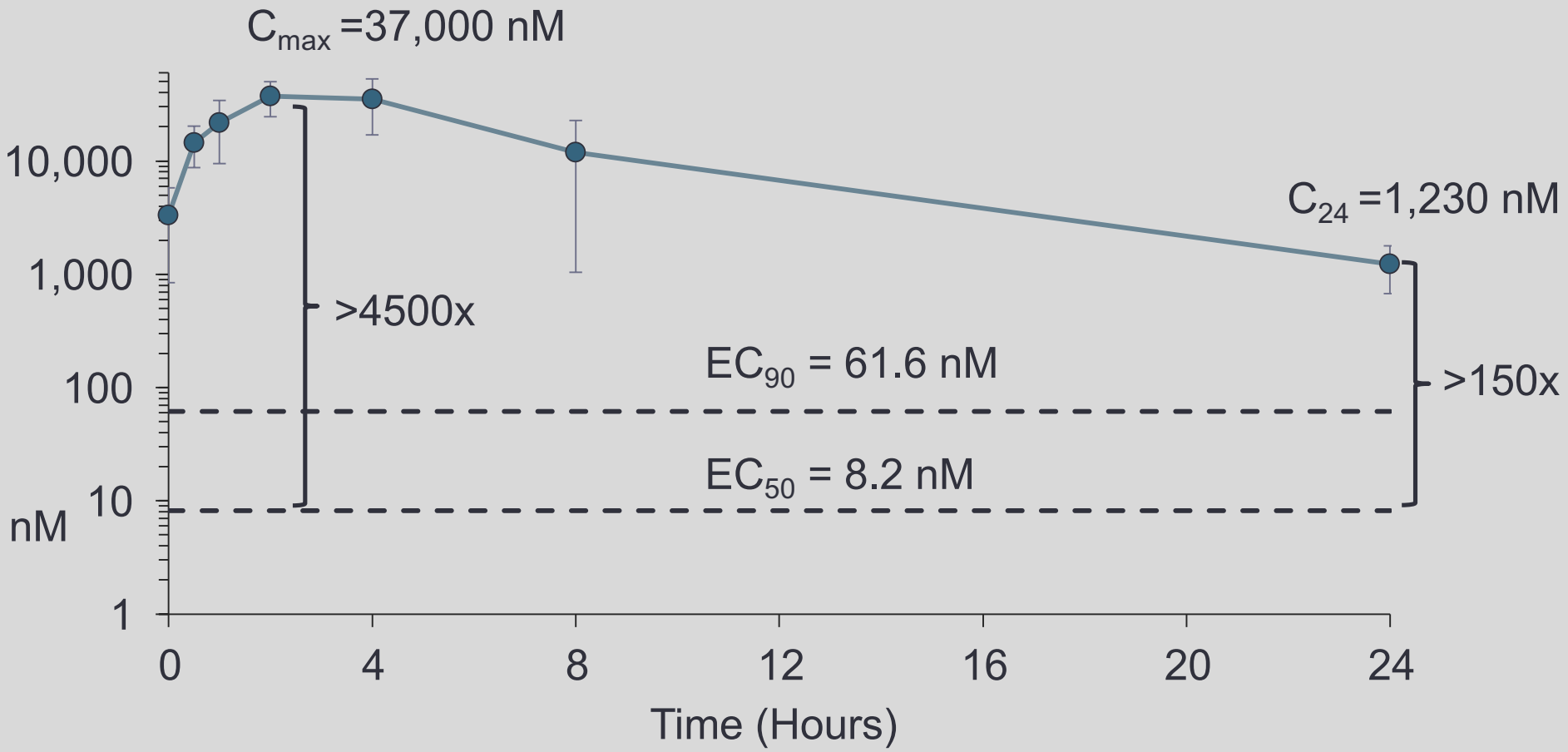
General Toxicity – 28-Day Studies in Rats and Monkeys

- Rat: No-observed-adverse-effect-level (NOAEL) of 300 mg/kg/day, high-dose level
  - Decreases in body weight and food consumption at the 300 mg/kg/day level was not considered adverse
- Monkey: No-observed-adverse-effect-level (NOAEL) was 100 mg/kg/day, mid-dose level
  - 300 mg/kg/day high-dose level adverse findings reversed upon dose reduction to 150 mg/kg/day

SOURCE: ATN-249 Repeat Dose Rat and Monkey General Toxicity Reports

28-Day Repeat Exposure in Monkey Toxicology Study

NOAEL (100mg/kg/day): Day 28



At NOAEL dose, ATN-249 provided C_{max} exposure >4500x and 24-h exposure (C_{24}) 150x >EC_{50} at day 28

SOURCE: ATN-249 28-Day Repeat Dose Monkey PK Report

Safety Pharmacology

Study	Sample	Mortality	AE
Functional Observational Battery (FOB)	Rat	None	None
Respiratory Functions	Rat	None	None
Cardiovascular Telemetry	Monkey	None	None

No mortality or adverse effects were observed on central nervous system, respiratory, and cardiovascular functions

SOURCE: ATN-249 Single Dose Rat and Monkey Safety Pharmacology Reports

Toxicology/Genotoxicity

Study	Result
Bacterial Reverse Mutation (Ames)	Negative
Chromosomal Aberration Assays	Negative
Bone Marrow Micronucleus Assay	Negative
Coagulation Studies	Negative

No genotoxicity or coagulation issues noted in a wide range of studies

SOURCE: ATN-249 Genotoxicity Reports

Conclusions and Discussions

- Positive preclinical study results of ATN-249:
  - **Potency**: ~10-fold greater plasma kallikrein inhibition vs. C1-INH
  - **Selectivity**: >2000-fold selective vs other serine proteases
  - **DMPK**: High 24-hour exposure, comprehensive drug recovery, no P450 liabilities
  - **Safety**:
    - NOAEL of 100 mg/kg/day established
    - No findings in all safety pharmacology studies
- ATN-249 demonstrated a wide therapeutic window with once-daily oral dosing potential
- Clinical studies are upcoming to assess the clinical safety and efficacy of ATN-249