

Preclinical and Early Clinical Evaluation of SPI-452, a New Pharmacokinetic Enhancer (PKE)

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Introduction

- Protease inhibitors (PIs) are a cornerstone of HAART
- Majority of PIs require PK boosting with ritonavir
 - Advantages
 - Increases drug exposure
 - Reduces dosing frequency and pill burden
 - Improves antiretroviral efficacy
 - Disadvantages
 - Increases GI side effects
 - Increases lipid levels
 - Risk of generating protease resistant mutants in non-PI containing regimens

Goals of the Sequoia PKE Program

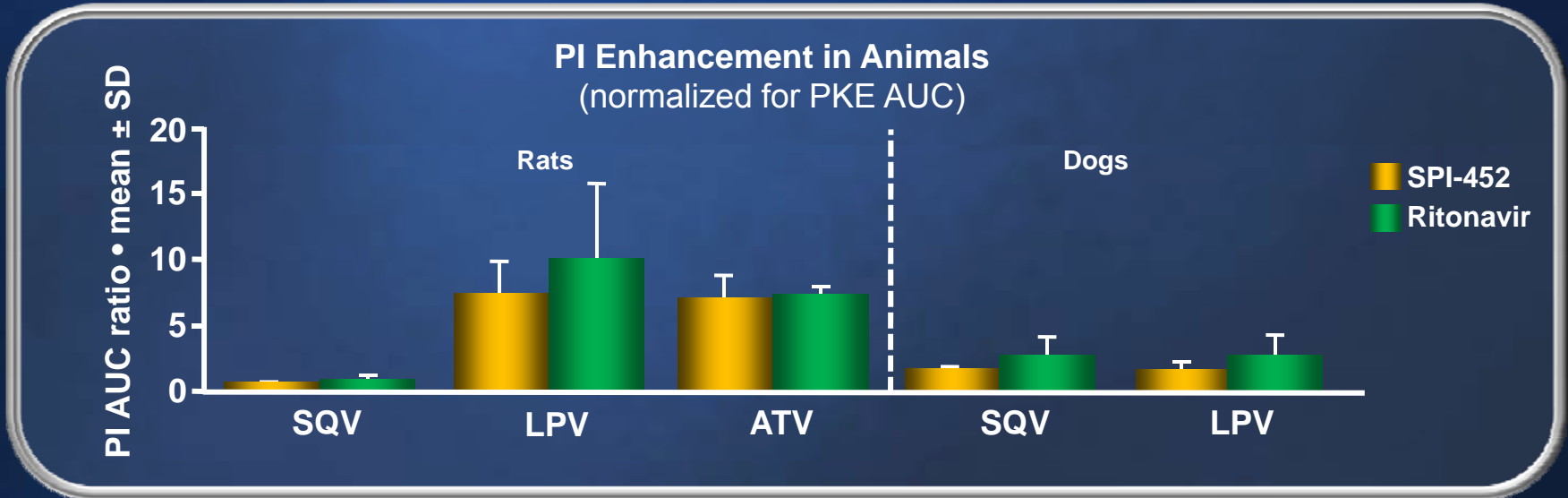
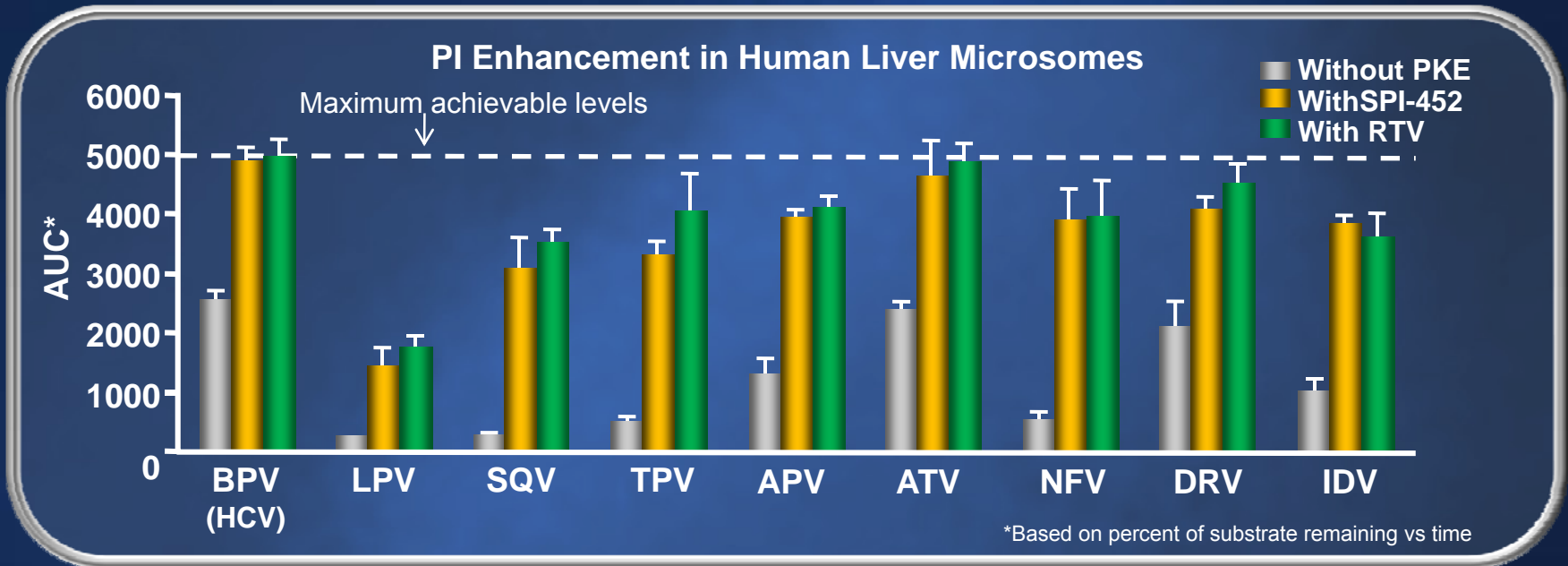
- Develop a potent and selective inhibitor of CYP3A4 that lacks inherent antiviral activity
- Enhance exposure of co-administered PIs comparable to ritonavir
- Favorable safety and tolerability profile
- Favorable metabolic/lipid profile
- Stand alone or fixed dose combination

SPI-452

Lead Candidate from PKE Program

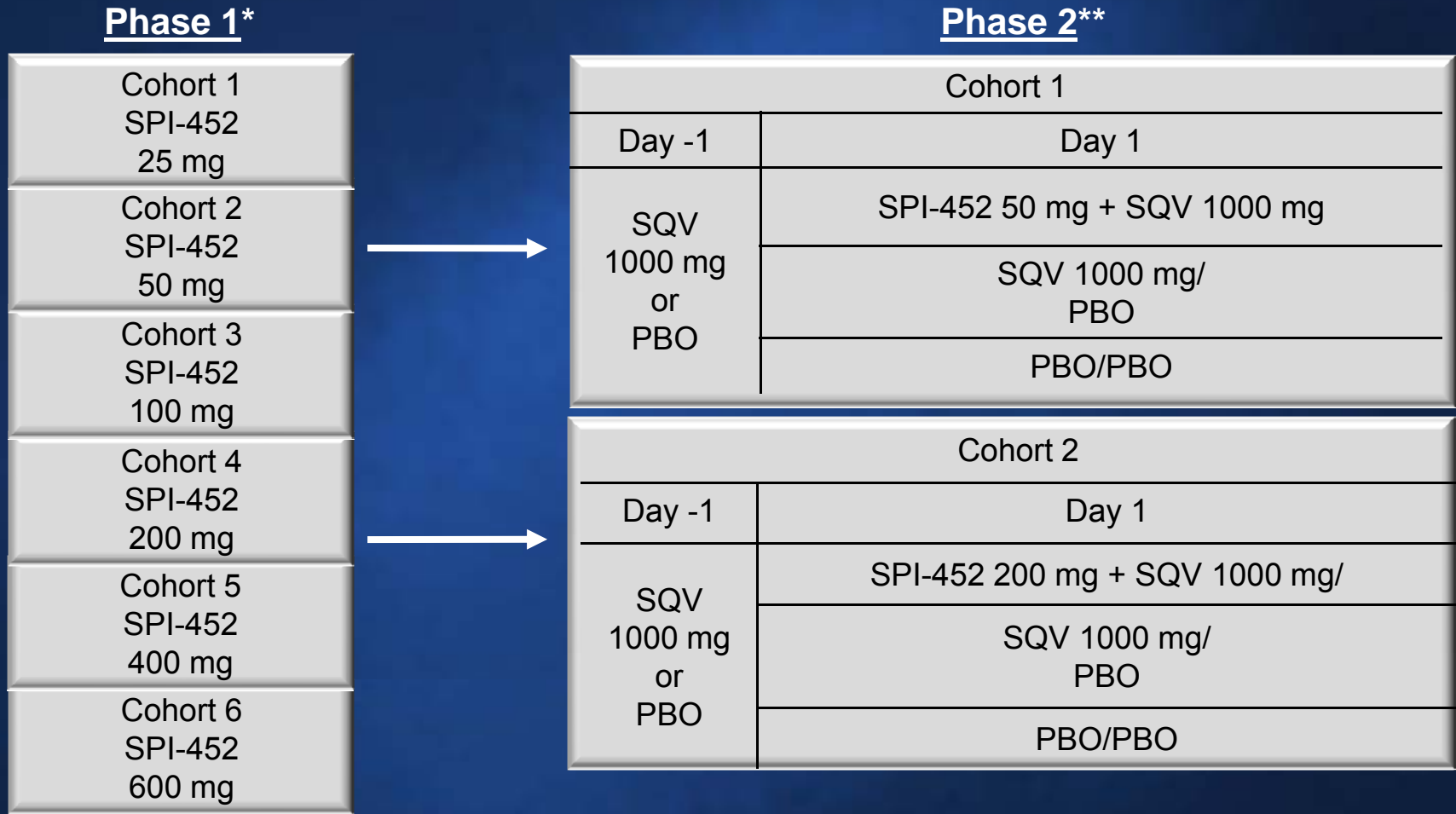
- Discovered through a targeted internal PKE research program
- Potent inhibitor of CYP3A
 - IC_{50} in microsomes \approx 10-20 nM
 - Preferential inhibition of CYP3A4/3A5
- No anti-HIV activity
- No alteration in anti-HIV activity of HAART drugs *in vitro*

PK Enhancement of PIs *In Vitro* and *In Vivo*



Study 0452-001: First Time in Humans

Study Design (N=58)



* Each cohort in Phase 1:

- SPI-452 (n=6)
- Placebo (n=2)

** Each cohort in Phase 2:

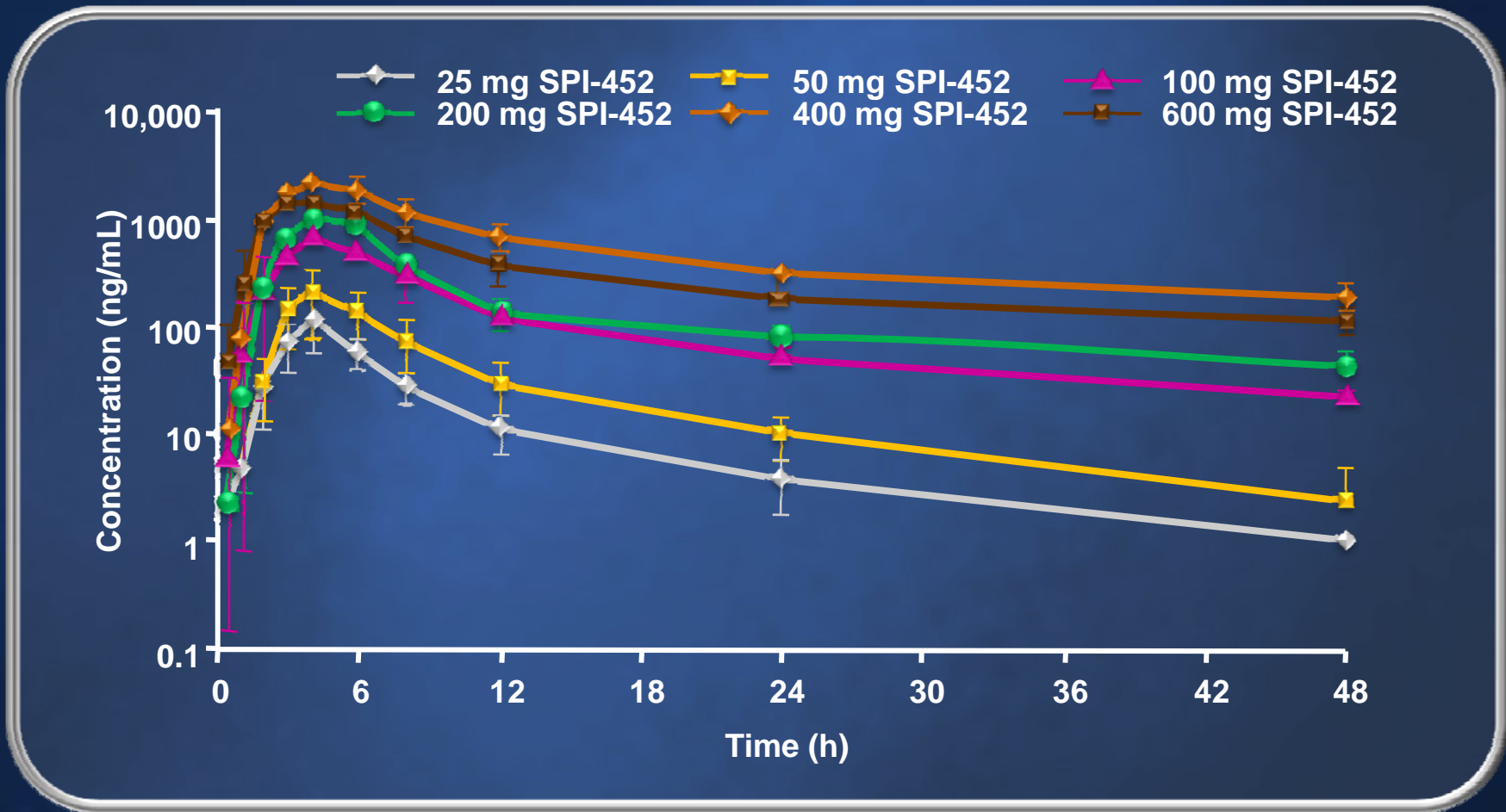
- SQV→SPI-452 + SQV (n=6)
- SQV→ SQV + PBO (n=2)
- PBO→ PBO + PBO (n=2)

Study 0452-001: First Time in Humans Safety

- SPI-452 was generally safe and well tolerated
 - No withdrawals due to study drug
 - No serious adverse events (SAEs)
 - Adverse events (AEs)
 - 19 subjects experienced ≥ 1 AE
 - Usually mild in severity
 - No pattern of body-system AEs
 - Headache (n=4) and pharyngitis (n=4) most common
 - No clinically relevant changes in ECG, vital signs, or clinical laboratory parameters

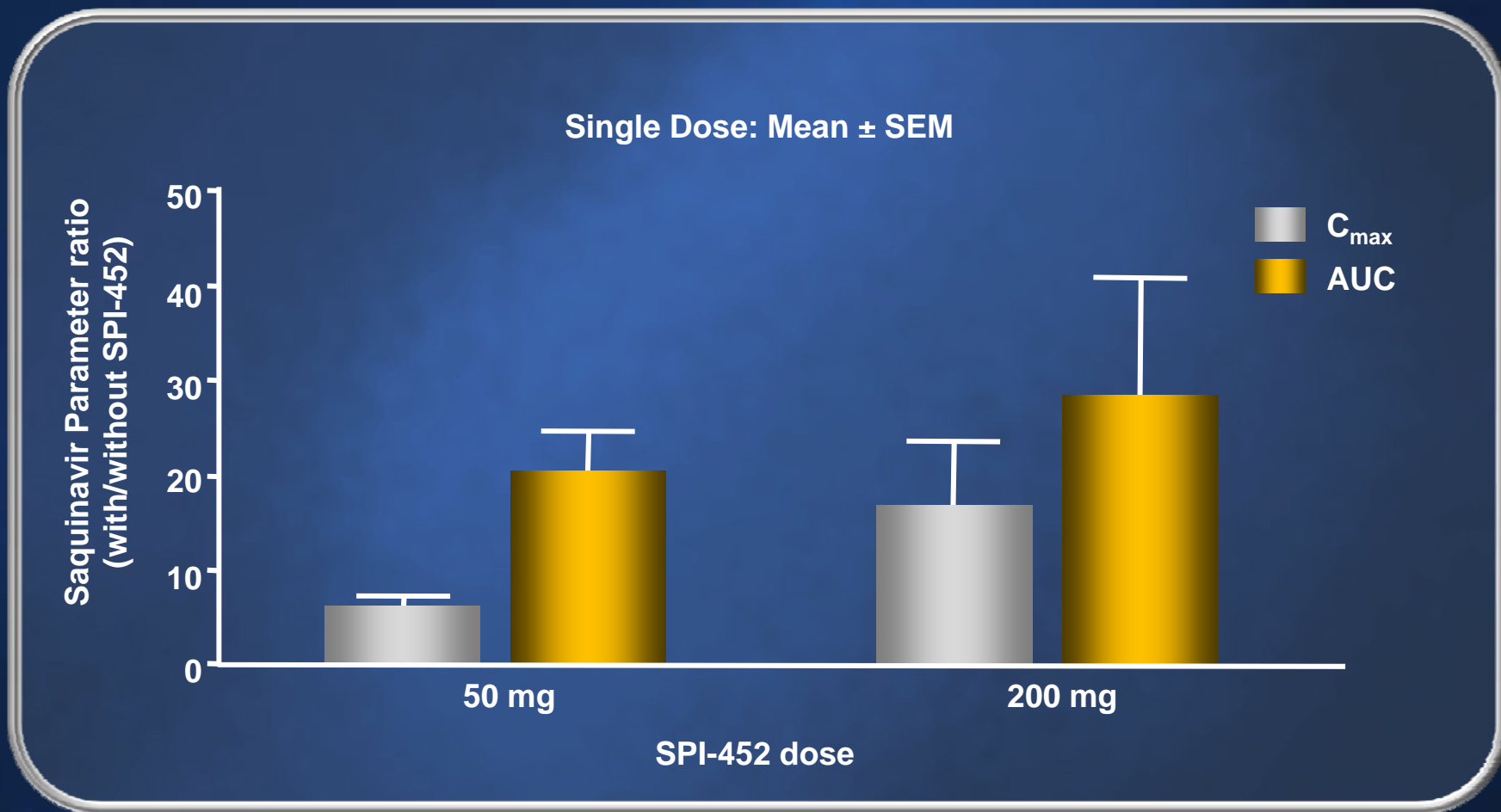
Study 0452-001: First Time in Humans

SPI-452 Mean Concentration-Time Profiles



Study 0452-001: First Time in Humans

SPI-452 Enhances Saquinavir Exposure



Study 0452-002: Proof of Clinical Concept

Study Design (N=67)

Day -7	Days -6 to -1	Days 1 to 14	Day 15	Day 16	Days 17 to 28
ATV 300 mg (n=6)	Washout	SPI-452 Alone	SPI-452 + ATV	ATV	Washout
DRV 600 mg (n=6)		SPI-452 Alone	SPI-452 + DRV	DRV	
PI PBO (n=6)		SPI-452 Alone	SPI-452 + PI PBO	PI PBO	
PI PBO (n=4)		PBO	PBO + PI PBO	PI PBO	

3 cohorts in the study. In each cohort: SPI-452 (n=18) or Placebo (n=4)

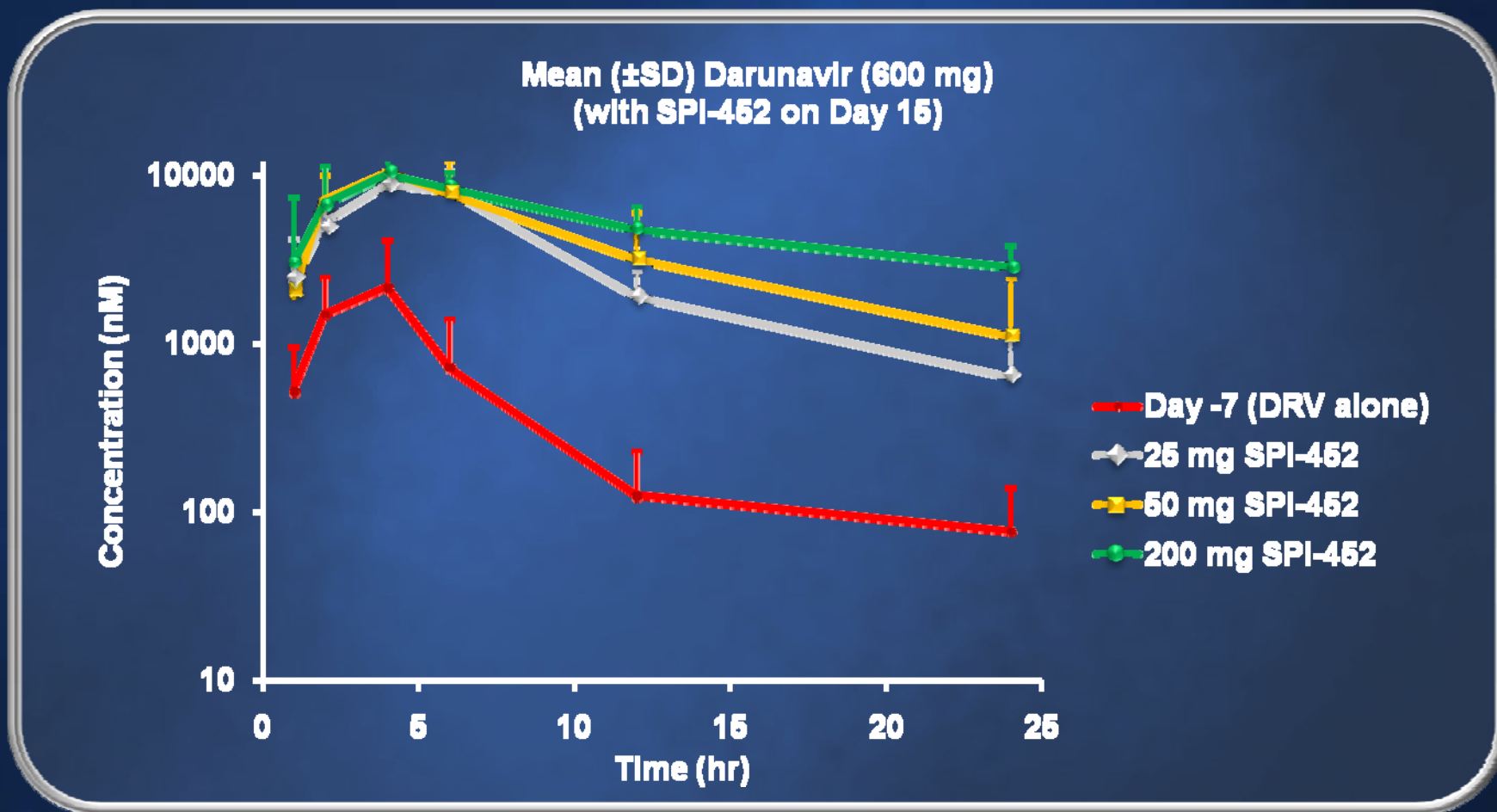
- Cohort 1: SPI-452 25 mg QD
- Cohort 2: SPI-452 50 mg QD
- Cohort 3: SPI-452 200 mg QD

Study 0452-002: Proof of Clinical Concept Safety

- SPI-452 was generally safe and well tolerated
 - No withdrawals due to study drug
 - No SAEs
 - AEs
 - 45 subjects experienced ≥ 1 AE
 - Usually mild in severity
 - No pattern of body-system AEs
 - Headache (n=17), nausea/emesis (n=11), and diarrhea (n=7) most common AEs
 - No clinically meaningful changes in ECG or clinical laboratory parameters
 - No statistically significant changes in triglyceride and LDL levels compared to placebo

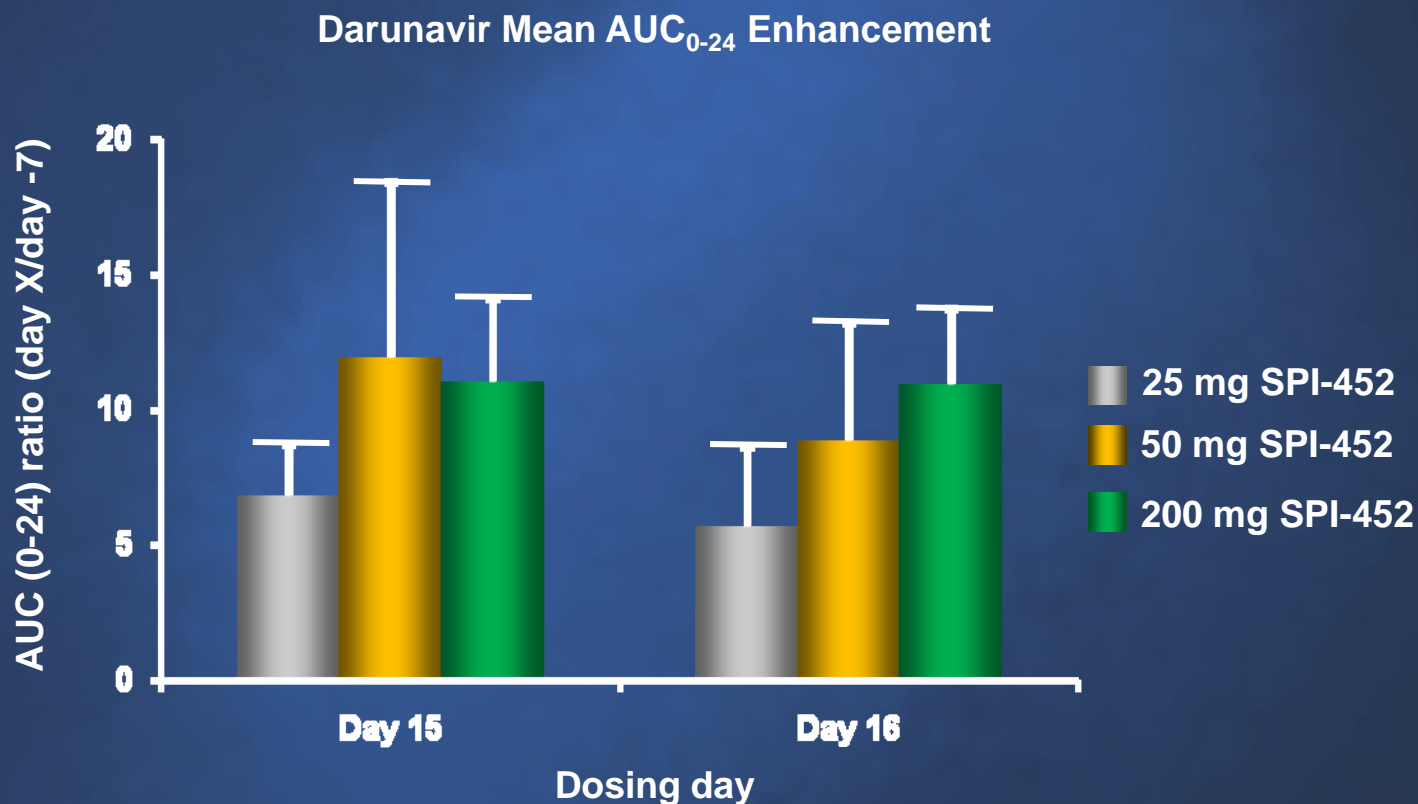
Study 0452-002: Proof of Clinical Concept

SPI-452 Enhances Darunavir Exposure



Study 0452-002: Proof of Clinical Concept

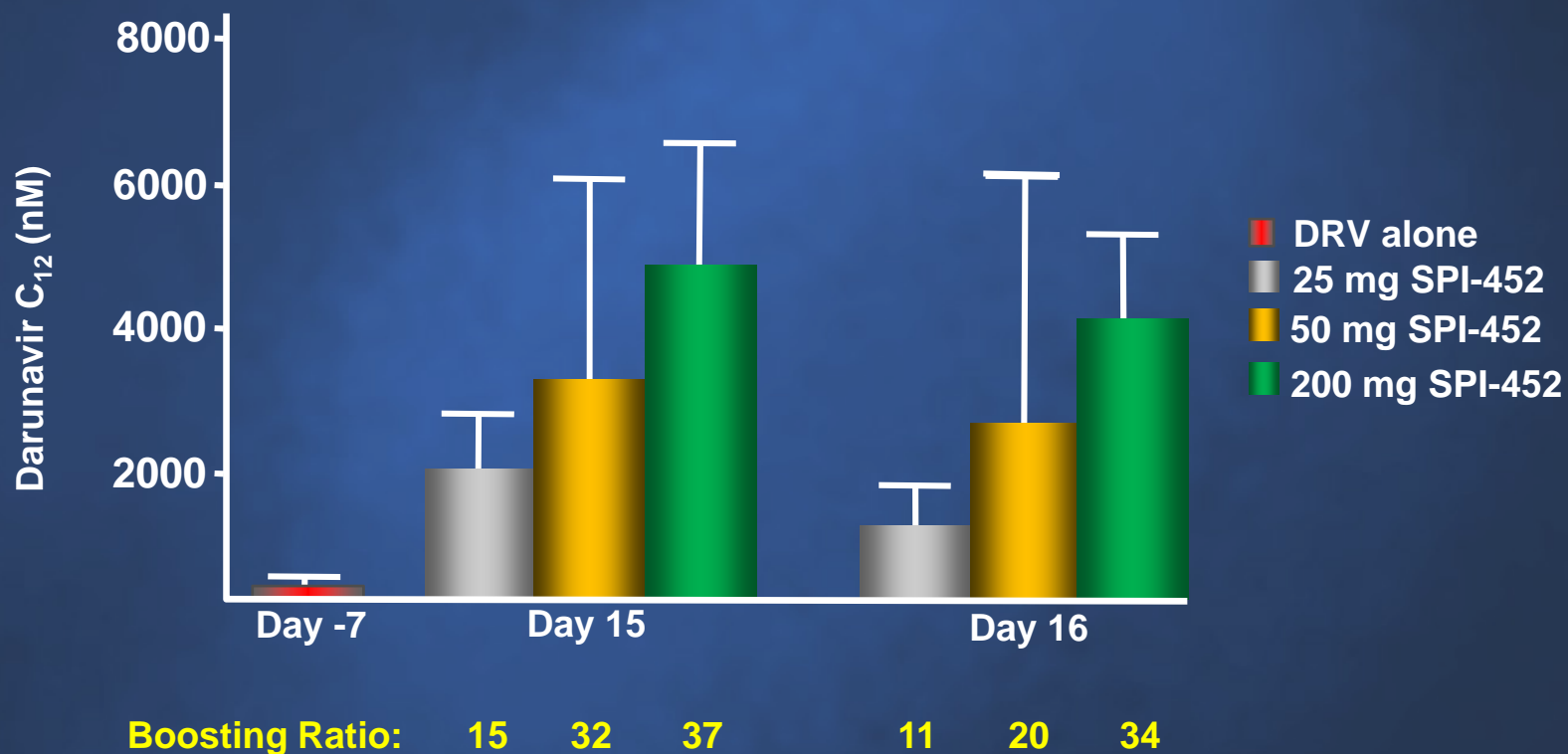
SPI-452 Enhances Darunavir Exposure (AUC)



Study 0452-002: Proof of Clinical Concept

SPI-452 Enhances Darunavir Exposure (C_{12})

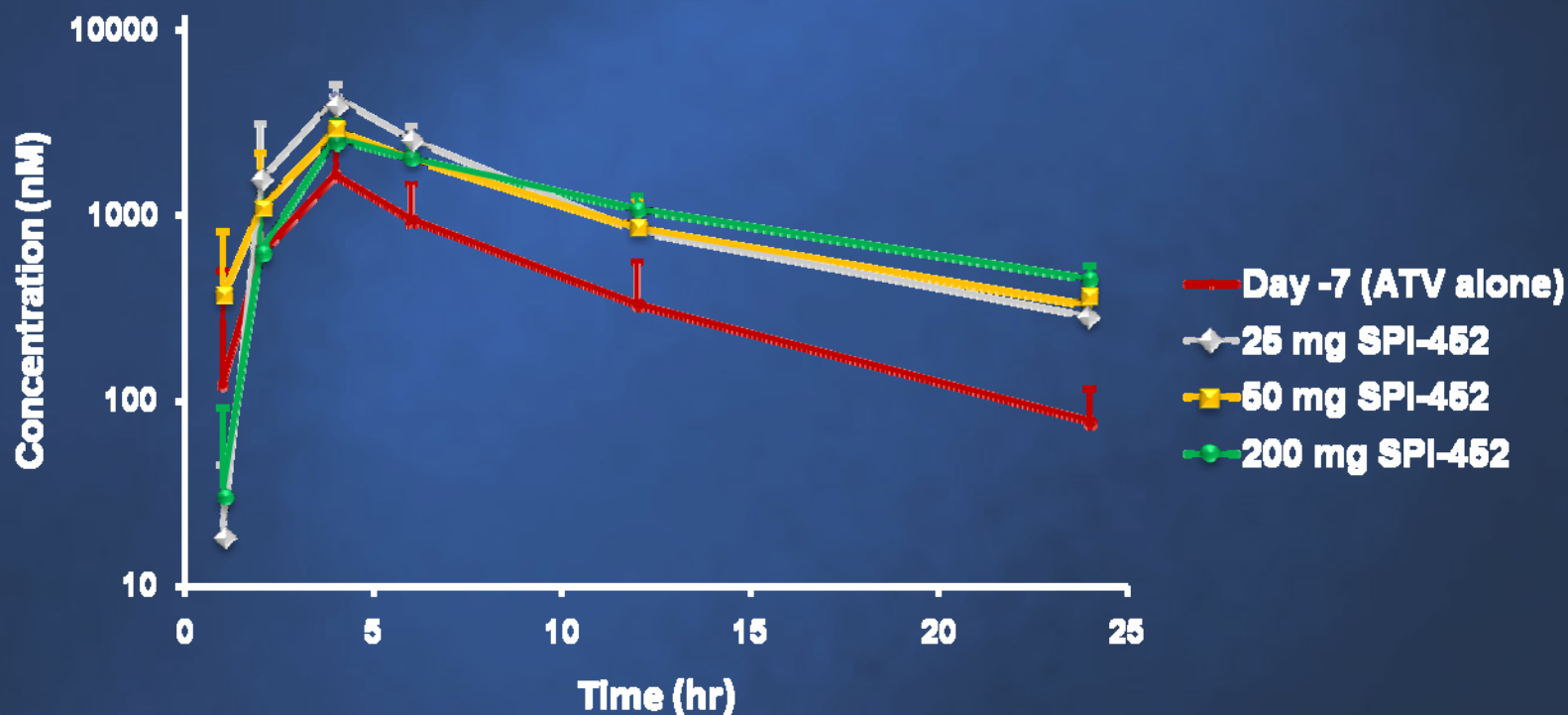
Darunavir Mean C_{12} Enhancement



Study 0452-002: Proof of Clinical Concept

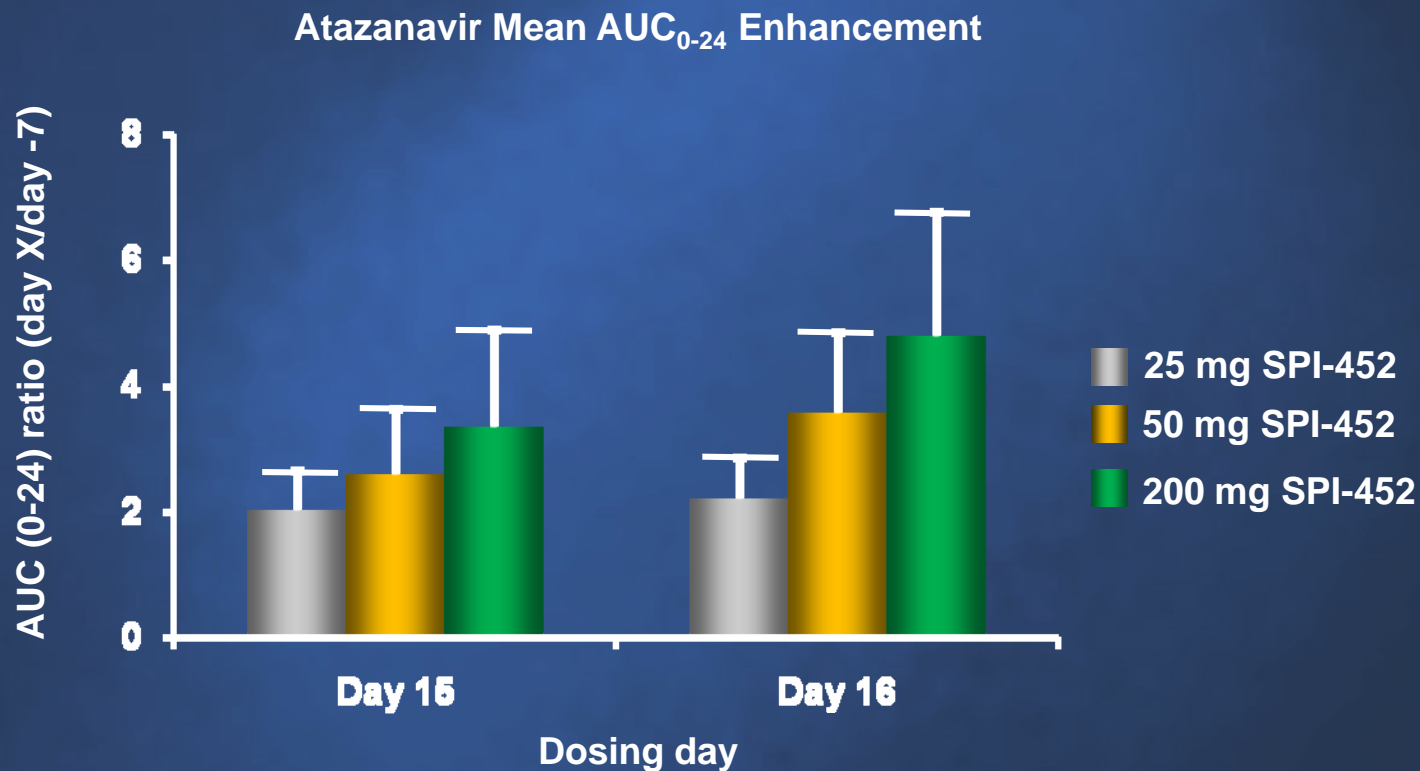
SPI-452 Enhances Atazanavir Exposure

Mean (\pm SD) Atazanavir (300 mg)
(with SPI-452 on Day 15)



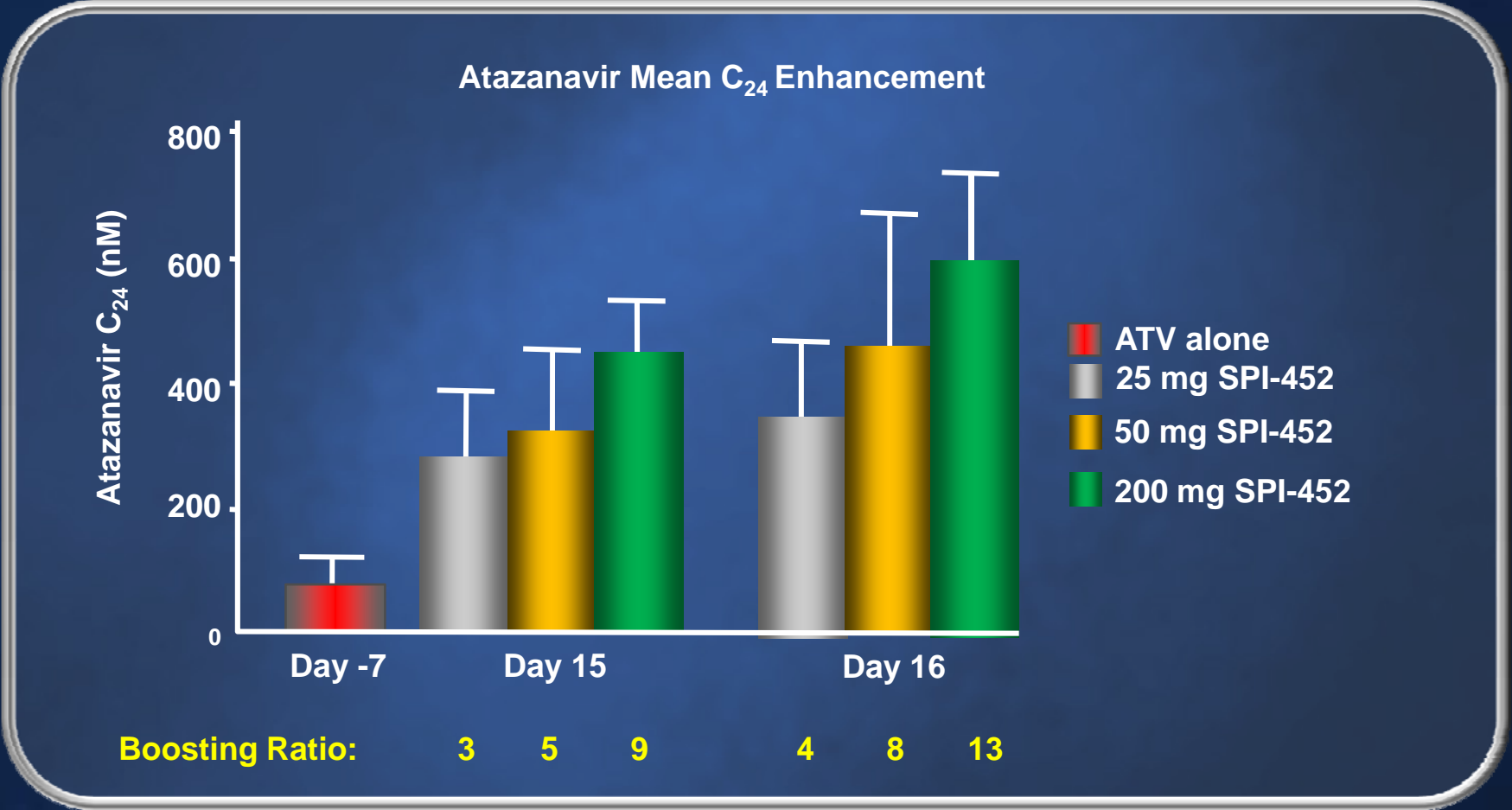
Study 0452-002: Proof of Clinical Concept

SPI-452 Enhances Atazanavir Exposure (AUC)



Study 0452-002: Proof of Clinical Concept

SPI-452 Enhances Atazanavir Exposure (C_{24})



Study 0452-002: Proof of Clinical Concept Summary

- SPI-452 was generally safe and well tolerated
- No statistically significant changes in triglyceride and LDL levels compared to placebo
- SPI-452 PK
 - Reached steady state by day 14
 - Accumulation of SPI-452 was slightly greater than linear with multiple dosing
- SPI-452 significantly enhanced systemic exposures of darunavir and atazanavir
- C_{\min} is the parameter most sensitive to SPI-452 enhancement

Conclusion

SPI-452 achieved all PKE Program goals:

- Potent and selective inhibitor of CYP3A4 that lacks inherent antiviral activity
- Favorable safety and tolerability profile
- Favorable metabolic/lipid profile
- Enhances exposure of co-administered PIs comparable to ritonavir

SPI-452 is a promising new agent that may expand future treatment options and enhance current standard of care