Pharmacokinetics of Scopolamine Intranasal gel Formulation (INSCOP) during Antiorthostatic Bedrest

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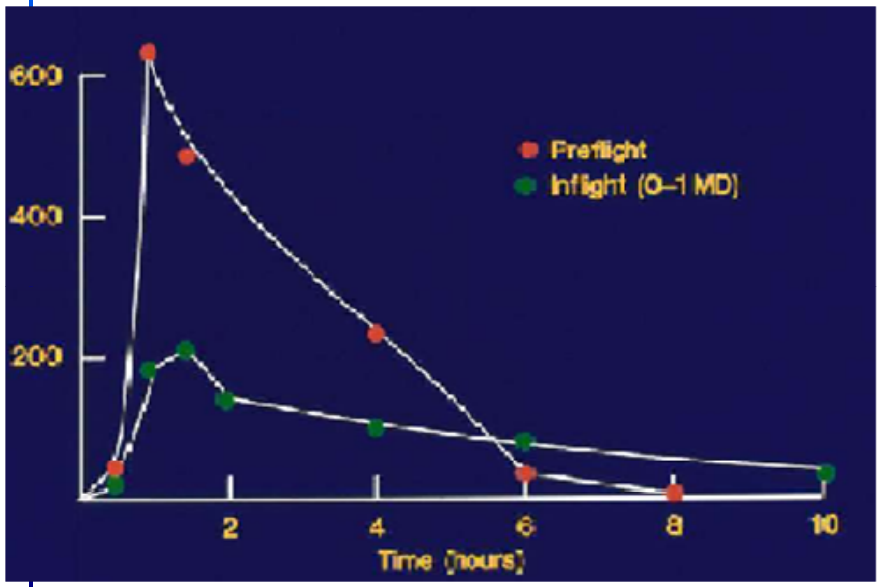
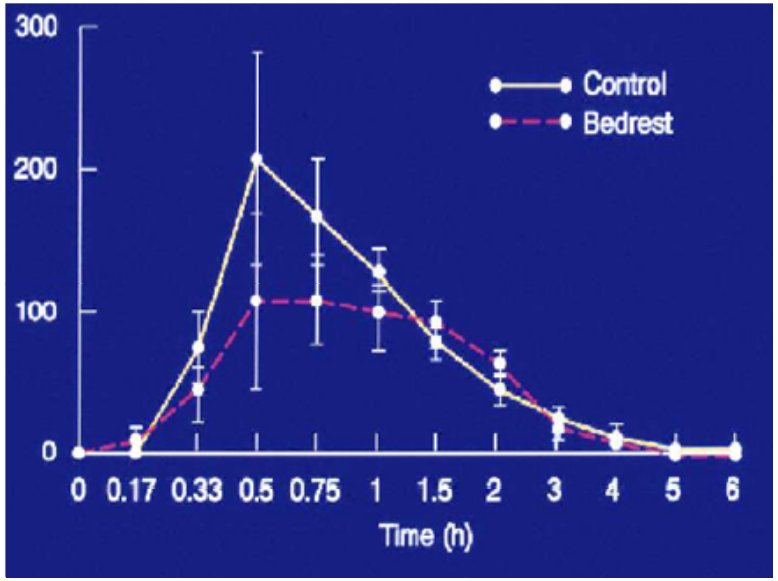
Introduction

- Space Motion sickness (SMS) is an age old problem for space travelers – on short and long duration space flight
- Oral antiemetics are not very effective in space due to poor bioavailability
- Scopolamine (SCOP) is the most frequently used drug by recreational travelers – patch, tablets available on the market
- Common side effects of antiemetics, in general, include drowsiness, sedation, dry mouth and reduced psychomotor performance
- Severity and persistence of side effects are often dose related
- Side effects can be detrimental in high performance demanding settings, e.g. space flight, military

The Oral Scopolamine Story

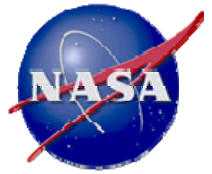


A representative saliva concentration –time profile in a crewmember



Mean Plasma concentration – time curve in normal subjects

Intranasal Scopolamine



- Oral, injectable and transdermal formulations of SCOP are either invasive, unsuitable or ineffective for the treatment of SMS
- Intranasal dosage form of scopolamine offers great promise for the treatment of MS on Earth and in space
- Advantages of intranasal dosage forms in general are:
  - Noninvasive
  - Rapid absorption facilitating rescue and treatment options with the same formulation
  - Enhanced and reliable bioavailability allowing precise and reduced dosing options

A First Step - INSCOP Drops Formulation Development

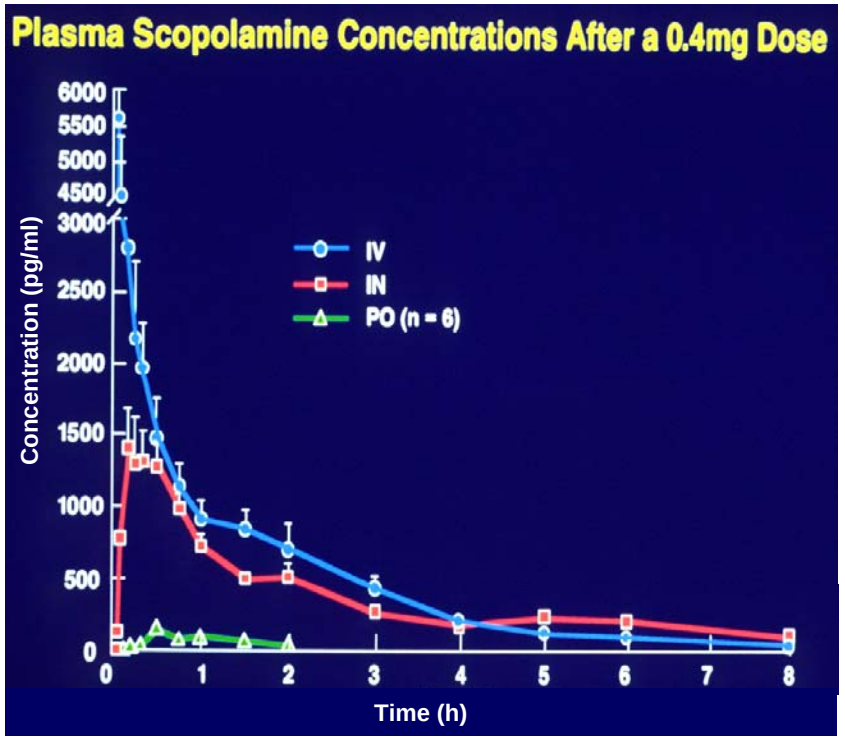
Results from a Phase I IND study showed 83% bioavailability of INSCOP versus 3.7% bioavailability of oral SCOP

Study Population: 12 healthy male subjects

Study Design: Randomized Crossover Design

Treatments: 0.4 mg of IV, PO, or IN Scopolamine

Blood Samples: Pre-dose, 0.42, 0.83, 0.17, 0.33, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12hr post dose.



Putcha L, Tietze KJ, Bourne DW, Parise CM, Hunter RP, Cintron NM. Bioavailability of intranasal scopolamine in normal subjects. J Pharm Sci. 1996 Aug;85(8):899-902.

Requirements for Therapeutics in Space

- Medications used for treatment in space must be commercial products for efficacy and safety reasons

- Investigational New drug (IND) protocols must strictly adhere to FDA guidelines for conducting Phase I - IV clinical trials to establish efficacy, safety and commercial potential

Pharmacotherapeutics of Intranasal Scopolamine – A NSBRI sponsored Drug Development project of INSCOP

Four FDA sponsored clinical trials were designed to characterize pharmacokinetics (PK) and pharmacodynamics, and evaluate the safety and efficacy of INSCOP

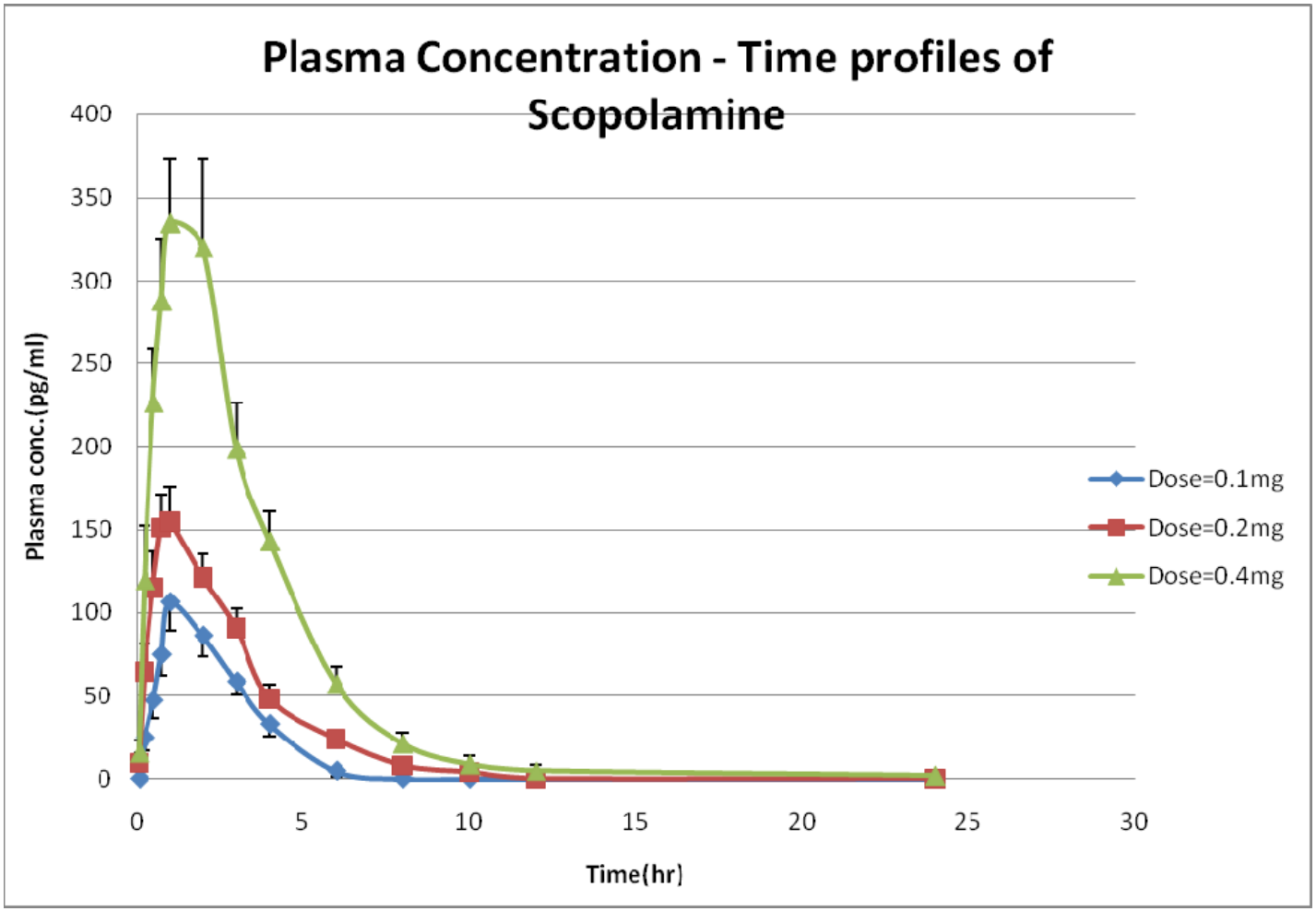
SPECIFIC AIMS	FDA PROTOCOL
Specific Aim # 1: Establish PK of INSCOP with three escalating dose levels of 0.1, 0.2 and 0.4 mg	INSCOP 002-A: Dose Ranging PK Study (MDS)
Specific Aim # 2: Perform a dose ranging Efficacy study of INSCOP	Dose/ Efficacy Studies: INSCOP 002-B (Dartmouth) INSCOP 002-D (NAMRL)
Specific Aim # 3: Determine if bioavailability and PD of IN SCOP are altered in a simulated microgravity environment	INSCOP 002-C: Bioavailability Study during ABR (MDS)

Specific Aim #1: Protocol 002-A

A Phase I, Randomized, Double-Blind, Placebo-Controlled, Dose Ranging Study of Pharmacokinetics and Pharmacodynamics of Intranasal Scopolamine

- Dose escalation of INSCOP at 0.1, 0.2 and 0.4 mg dose levels
- 12 normal healthy subjects (6 male/6 female) received INSCOP in a placebo-controlled randomized crossover design
- Assessment of primary PK parameters of INSCOP as a function of dose

Results

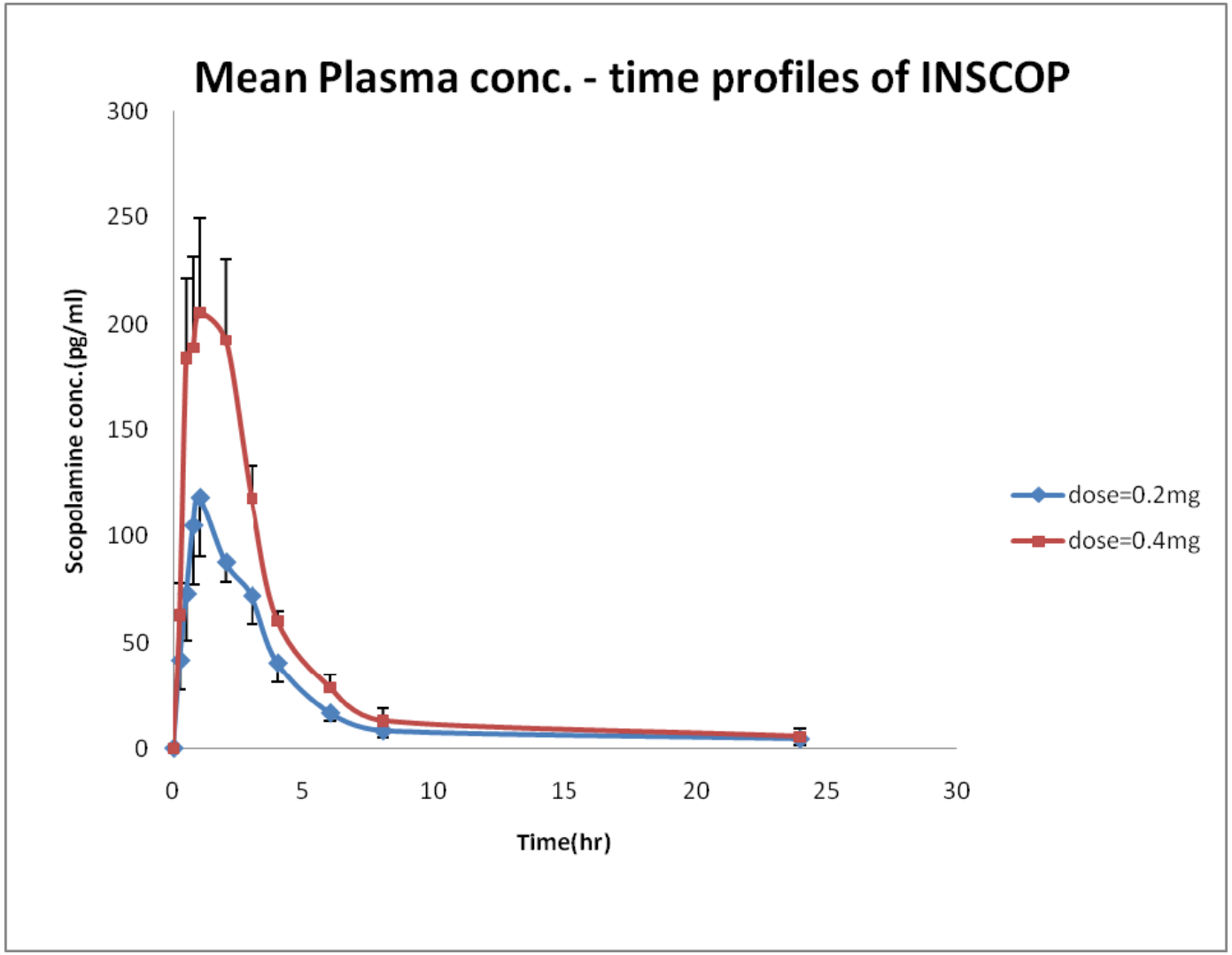

Plasma Concentration - Time profiles of Scopolamine
Plasma conc.(pg/ml)
400
350
300
250
200
150
100
50
0
0
5
10
15
20
25
30
Time(hr)
Dose=0.1mg
Dose=0.2mg
Dose=0.4mg

Specific Aim #2: Protocol 002-B

A Phase II, Randomized, Double-Blind, Placebo-Controlled, Efficacy Study of Intranasal Scopolamine

- Clinical efficacy study with 0.2 and 0.4 mg and INSCOP given as pre-treatment for motion sickness induced by off-axis Vertical Rotation Chair (VRC)
- 18 male/ female, motion sickness susceptible subjects
- Establish concentrations of INSCOP for efficacy as well as assess PK (10 subjects ONLY) of the two doses of INSCOP

Results


Mean Plasma conc. - time profiles of INSCOP
Scopolamine conc.(pg/ml)
300
250
200
150
100
50
0
0
5
10
15
20
25
30
Time(hr)
dose=0.2mg
dose=0.4mg

Specific Aim #3: Protocol 002-C

A Phase II, Randomized, Double-Blind, Bioavailability Study of Intranasal Scopolamine in a Simulated Microgravity Environment

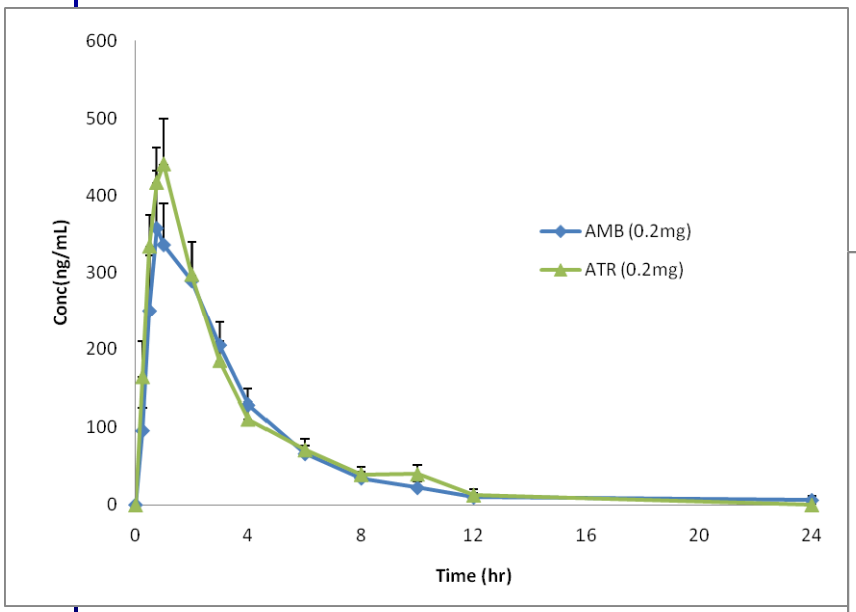
- Estimate the bioavailability of a 0.2 mg dose and 0.4 mg dose of INSCOP during ambulation (AMB) and simulated microgravity, Antiorthostatic Bed Rest (ABR)

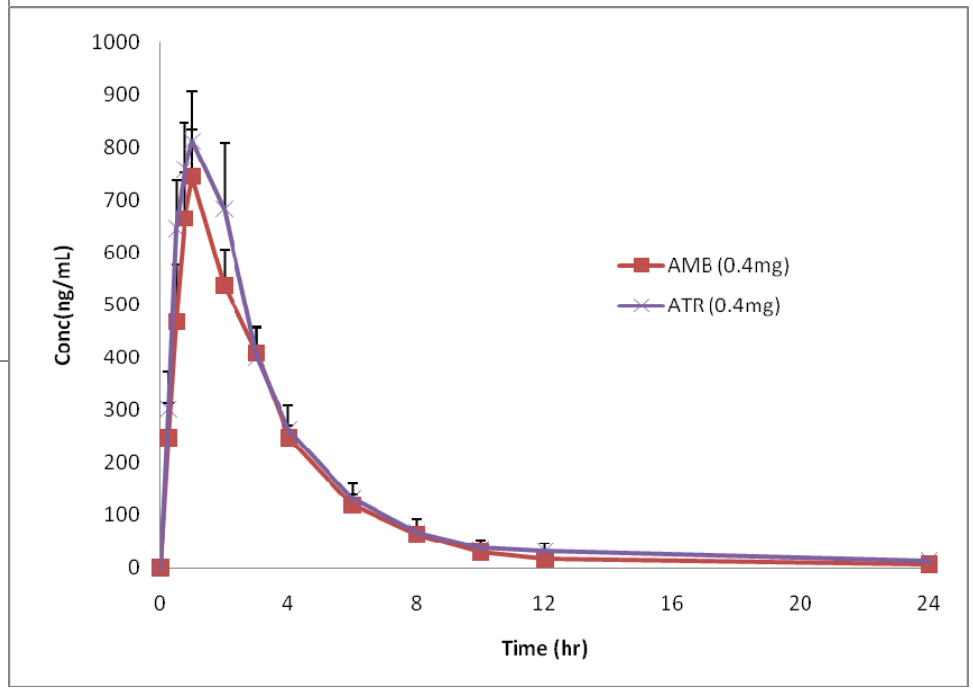
- 12 normal healthy subjects (6 male/ 6 female) received INSCOP in a four-way crossover design

- Evaluate PK/PD, safety and side effect profile of the two doses during AMB vs. ABR

Results

Concentration – time profiles of scopolamine in plasma



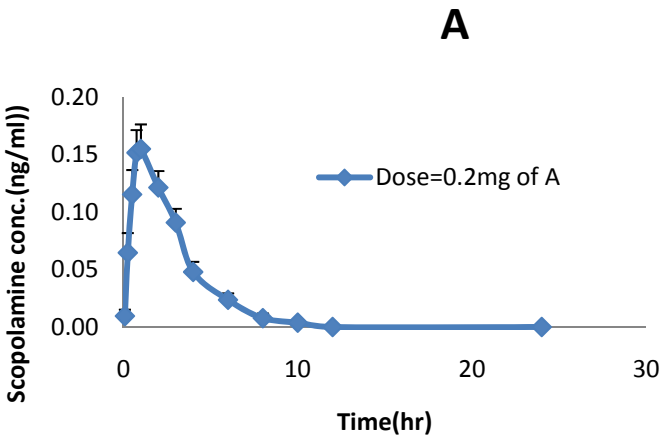


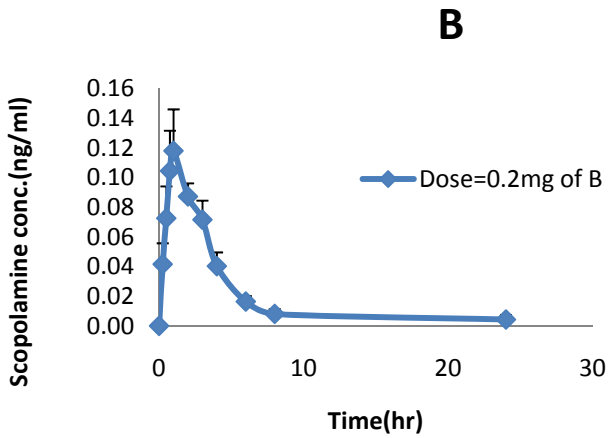
Primary PK Parameters

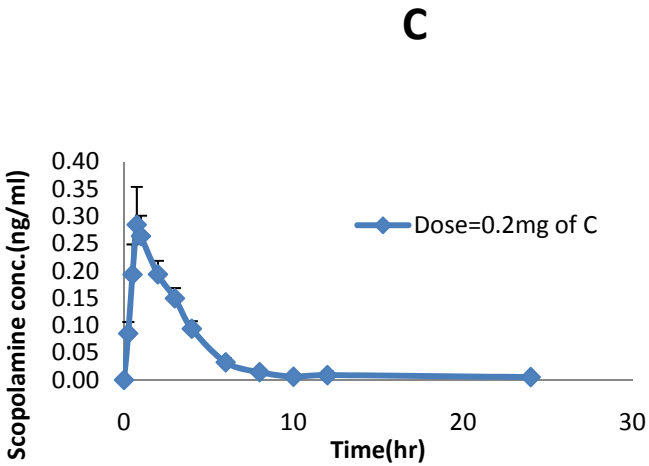
Parameters (Mean±SE)	Units	Dose(mg)			
		0.2		0.4	
		AMB	ABR	AMB	ABR
Cmax/D	pg/ml*mg	2.24±0.30	2.25±0.27	1.99±0.27	2.43±0.26*
Tmax	h	1.27±0.23	0.83±0.06	1.04±0.18	0.96±0.11
AUC_{inf}/D	h*pg/mL*mg	9.02±1.72	7.81±1.14	7.14±1.49	9.47±1.66**
V_s	L	578.03±93.55	545.96±49.82	568.90±75.37	773.91±209.35
Cl_s	L/h	141.70±16.45	156.36±20.22	180.70±22.40	128.20±14.01*
$t_{½}$	h	3.23±0.56	2.80±0.33	3.14±1.26	5.02±1.41

*P<0.05
**P<0.005

Comparative Profiles







PK Results (002 A)

- **Dose-related nonlinearity between 0.2 and 0.4 with clinically significant primary PK parameters, Cmax and AUC**

- **Dose and dosing intervals may be adjusted to account for nonlinearity at higher doses**

PK Results (002 C)

- No difference between AMB and ABR in PK parameters after 0.2 mg dose
- Cls decreased with a concomitant increase in Cmax and AUC during ABR after 0.4 mg dose
- This difference in AUC and Cls at the higher but not the lower dose during ABR is in agreement with the nonlinear kinetics with dose observed at these doses (002 A)
- Dosing adjustment may be required for treatment with INSCOP in space

Overall Results

- **Inter-site differences in profiles – may be a result of dosing discrepancies between study sites**

- **The dosage form for A and B are from a different vendor than for C**

- **Data for all protocols (0.2 and 0.4 ambulatory) will be pooled for obtaining statistical rigor for modeling**

Data Analysis in Progress

Extremely Rich data facilitating complex analysis options – Some trend analysis and interpretation currently in progress with respect to:

PK

- **Gender differences**
- **Dose – related metabolism differences**
- **PK modeling combining all ambulatory subjects data**
- **Plasma/saliva simultaneous fitting and correlation**
- **Metabolite kinetics**

Data Analysis in Progress

PD Dose – Effect analysis with

- **BP, HR data**

- **ARES Performance Parameters**
  - **Reaction time**
  - **Accuracy**
  - **Short and running memory recall**

PK/PD Modeling with applicable response parameters

Stay tuned for next update!