CONFIDENTIAL

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Development of a Loxapine Nasal Powder: Leveraging a 505(b)(2) Regulatory Pathway and PK Bridging to Enable At-Home Prevention of Acute Agitation

Paul Shields

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IPAC-RS International Pharmaceutical Aerosol Consortium on Regulation & Science

NASAL INNOVATION FORUM

Delivering solutions, shaping the future.

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Acute Agitation

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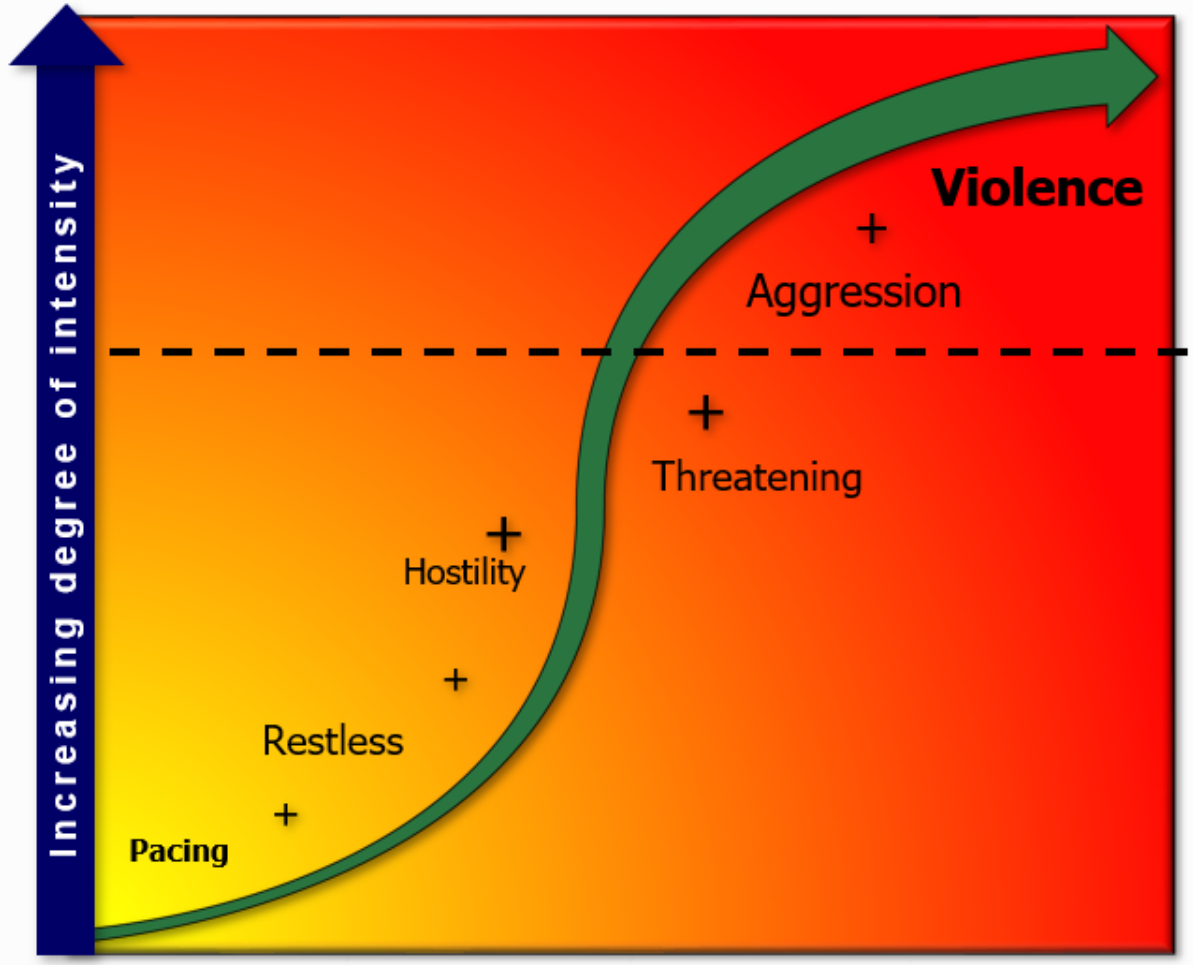
Acute Agitation

- Acute Agitation has multiple and varied definitions[1]
  - *DSM-IV* defines psychomotor agitation as excessive motor activity associated with a feeling of inner tension[2]
- Common component of psychiatric disorders such as bipolar disorder and schizophrenia[1]
  - Bipolar disorder
    - Agitation is a *DSM-IV* diagnostic criterion
    - Frequently observed in manic states
  - Schizophrenia
    - Associated with increased risk of aggression
    - Aggression is more common in male patients, those with disorganized schizophrenia subtype, and those with psychosis including delusions and disorganized thinking

1. Sachs GS. *J Clin Psychiatry*. 2006;67(suppl 10):5-12.
2. American Psychiatric Association. DSM-IV-TR. Arlington, VA: APA; 2000.

Agitation Intensification Escalation to Violence



Severe agitation
Common in schizophrenia, schizoaffective disorder, bipolar disorder[1]

Management goal for agitation
Intervene early to prevent escalation of agitation to violence[1]

1. Battaglia J. *Drugs*. 2005;65:1207-1222. Rossi J, Swan MC. *Emerg Med Clin N Am*. 2010;28:235-256.

Approved products are for in-patient setting

Acute Agitation Segments

Acute Agitation Market

Out-Patient Segment

- At home setting – majority of episodes
- No medication for AA / high unmet need
- ER and police are common options
- AA can lead to catastrophic outcomes

In-Patient Segment

- Hospitals and in-patient psychiatric facilities encounter AA routinely
- Low-cost IM treatment options available
- Sedation and restraints can be difficult to use
- Cost controls are key priorities

Out-Patient value proposition appears very strong:

- Prevent mental health encounter with police, potential for harm and jail
- Avert ER visit and potential hospitalization / minimize law enforcement involvement
- Provides first and only “agitation rescue” treatment option

Adasuve STACCATO (Loxapine)
Approved Jan 2012 / Launched Mar 2014

BIGALMI™ (dexmedetomidine) sublingual film
April 2022

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Home Based Treatment of Acute Agitation is a Game Changer

- Product A Reaction:

"Adasuve w/o REMS you got a winner"

"OUTSTANDING"

"I see as something that should be in everyone's medicine cabinet"

- Loxapine is a good choice for AA
  - Has long history of AA treatment
  - Approved use in Adasuve is an advantage
  - 1st gen anti-psych but most like 2nd gen
  - Episodic use should limit any possible 1st gen AE's
  - As good as any medication for this indication (olanzapine & ziprasidone)
- If a patient asks for this medication, they will get it

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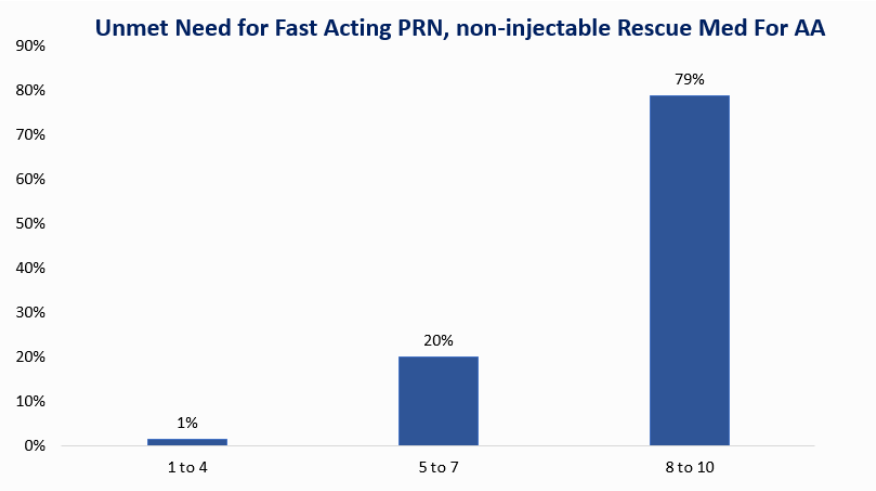
Quantitative Market Research Validates KOL View

National Quantitative Market on Acute Agitation:

- On-line internet survey fielded June 2021
  - 75 Board Certified Psychiatrist in USA
  - Managing and treating Bi-polar and Schizophrenia patients
  - 80% avg. time spent in Out-Patient setting
  - 102 patients with Bi-polar and Schizophrenia seen / month
  - 21 avg. years in practices



Initial Reaction is Very Favorable for Product A

Negative		Neutral		Positive	
Count	Verbatim	Count	Verbatim	Count	Verbatim
1	Expensive	15	Interesting	9	Needed
1	Not sure if it is different then PO already in-use	1	Wait to see how it works & cost	9	Promising or Positive
1	Skeptical	1	Copay	7	Great
1	Useless	1	New	6	Helpful or Useful
1	Unnecessary	1	Can it be abused?	4	Impressive or Valuable
				3	Awesome
				3	Breakthrough
				3	WOW! Most needed
				2	Excellent Much Needed
				1	Convenient
				1	Game Changer

Overall conclusion: market research indicates a very significant opportunity

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505(b)(2)

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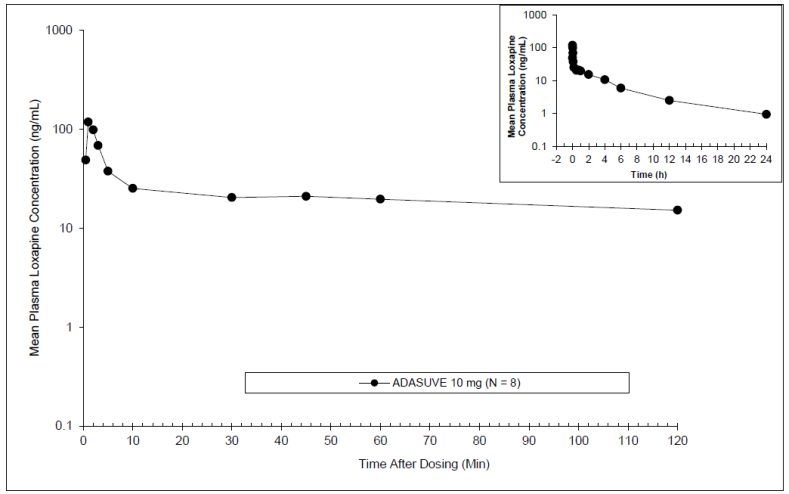
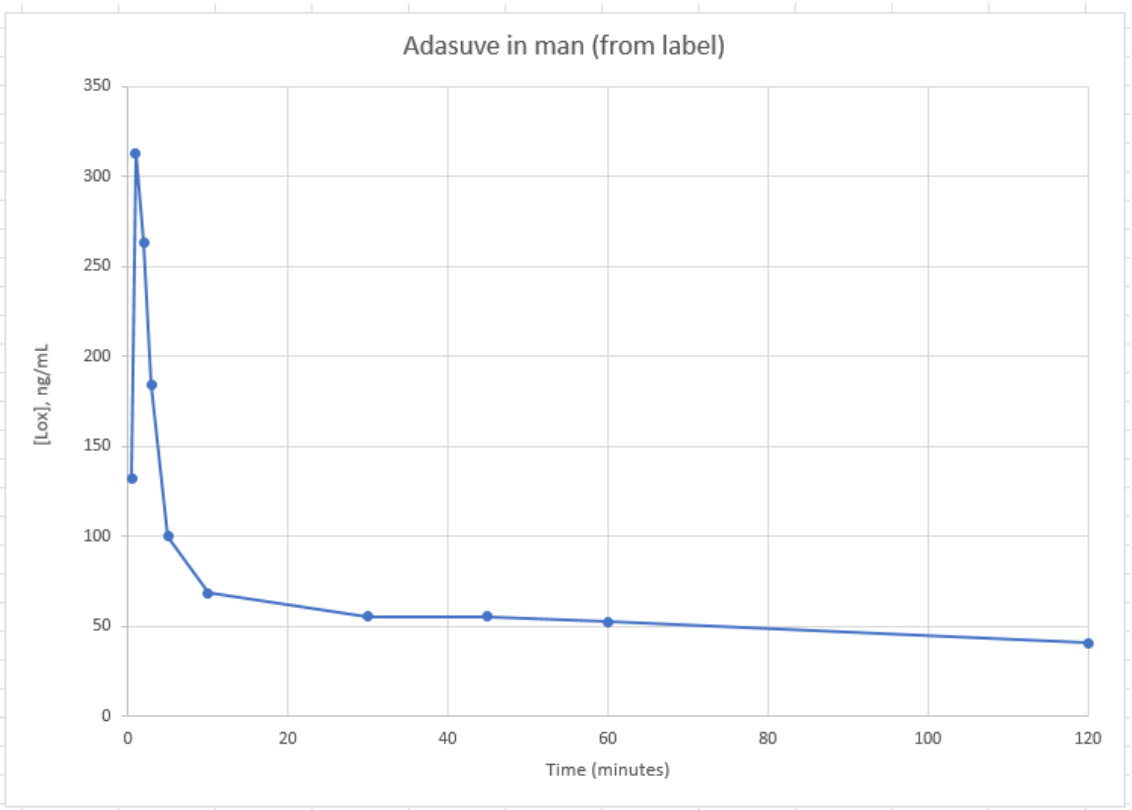
Adasuve

adasuve®
(loxapine) inhalation powder

Figure 8. **Mean Plasma Concentrations of Loxapine following Single-Dose Administration ADASUVE 10 mg in Healthy Subjects**





A BE analysis requires two parameters – typically Cmax and AUC

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Adasuve

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
022549Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DID THE SUBMITTED STUDY 103 COMPARING CLINICAL VERSION 2 TO COMMERCIAL VERSION 1 MEET THE REGULATORY REQUIREMENTS TO BE CONSIDERED A BIOEQUIVALENCE STUDY?

No, BE analysis requires that at least two parameters be evaluated (i.e., AUCinf and Cmax). For study 103 Cmax was not evaluated as a primary metric therefore, data from this study can only be used to determine equivalent exposure not true BE.

WHAT ARE THE PARAMETERS FOR DETERMINING EQUIVALENT EXPOSURE FOR THIS NDA?

The primary parameter for determination of equivalent exposure is AUC(0-2h). A secondary parameter would be AUCinf.

WHY IS AUC(0-2hr) CONSIDERED THE PRIMARY METRIC FOR AGITATION?

Agitation is a condition that requires an immediate onset of clinical intervention. Therefore, based upon the desired Clinical response it was decided by the Division of Psychiatry Drug Products that early exposure within 2 hrs was most relevant. Cmax was not expected to be Bioequivalent since it is a discrete variable that occurs within 2 min of drug administration, which makes it difficult to accurately measure. It was considered a secondary measure.

Spray Dried Formulations

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Loxapine Succinate alone

Test	Result	
Assay	98.4%	
Total Impurities	None detected	
Bulk Powder Particle Size Distribution (Laser Diffraction)	D10 (µm):	3.97
	D50 (µm):	15.51
	D90 (µm):	26.98
	Particles < 10.5 µm:	26.7%
Aerodynamic Particle Size Distribution (10 mg fill, as loxapine) (ACI with 2L Expansion Chamber)	Impactor Size Mass (µg / % w/w)	209.4 µg (2.2%)
Water Content (Karl Fischer titration)	1.71%	
Single Actuation Content (As loxapine base, n=10)	Mean: 2.63 mg (88%) Range: 2.19 – 2.81 mg (73-94%) SD: 0.20 mg (7%)	

Loxapine Succinate / HPMC / Mannitol

30% Loxapine Succinate, USP
30% HPMC (Pharmacoat 606)
40% Mannitol (Pearlitol 160C)

Test	Result	
Assay	100.6%	
Total Impurities	None detected	
Bulk Powder Particle Size Distribution (Laser Diffraction)	D10 (µm):	15.57
	D50 (µm):	24.39
	D90 (µm):	36.48
	Particles < 10.5 µm:	2.43%
Aerodynamic Particle Size Distribution (10 mg fill, as loxapine) (ACI with 2L Expansion Chamber)	Impactor Size Mass (µg / % w/w)	18.9 µg (0.2%)
Water Content (Karl Fischer titration)	2.08	
Single Actuation Content (As loxapine base, n=10)	Mean: 2.86 mg (95%) Range: 2.70 – 2.99 mg (90-100%) SD: 0.08 mg (3%)	

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Loxapine Succinate / HPMC / Mannitol / $CaCl_2$

25.3% Loxapine Succinate, USP
25.3% HPMC (Pharmacoat 606)
33.9% Mannitol (Pearlitol 160C)
15.5% Calcium Chloride Dihydrate

Test	Result	
Assay (RP-HPLC)	98.2%	
Total Impurities (RP-HPLC)	None detected	
Residual Methanol (HS-GC)	10.0 ppm	
Bulk Powder Particle Size Distribution (Laser Diffraction)	D10 (µm):	15.82
	D50 (µm):	27.88
	D90 (µm):	41.03
	Particles < 10.5 µm:	6.03%
Aerodynamic Particle Size Distribution (ACI with 2L Expansion Chamber)	Impactor Size Mass (µg / % w/w)	74 µg (0.7%)
Water Content (Karl Fischer titration)	2.88%	

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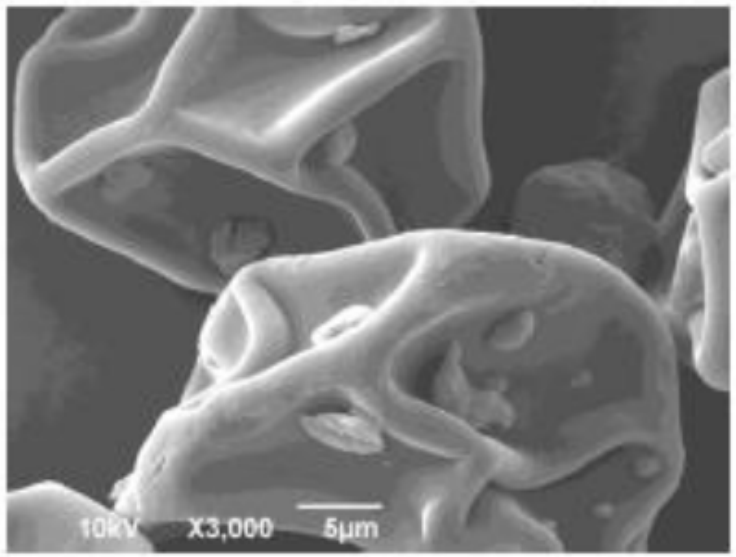
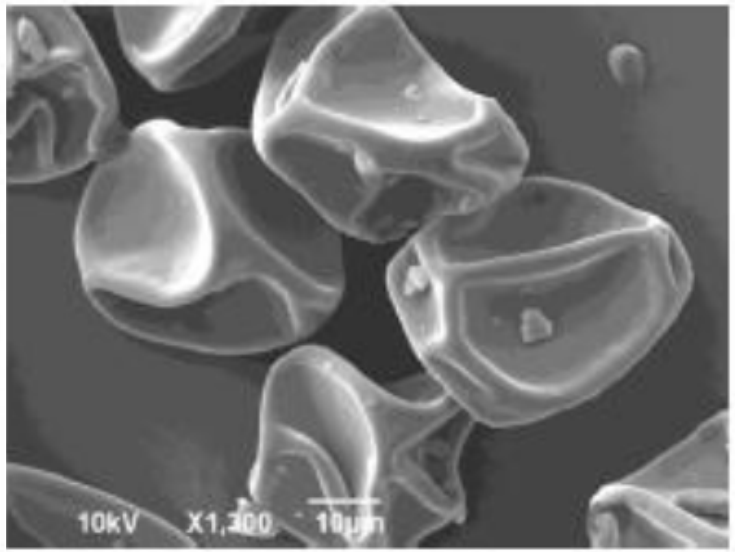
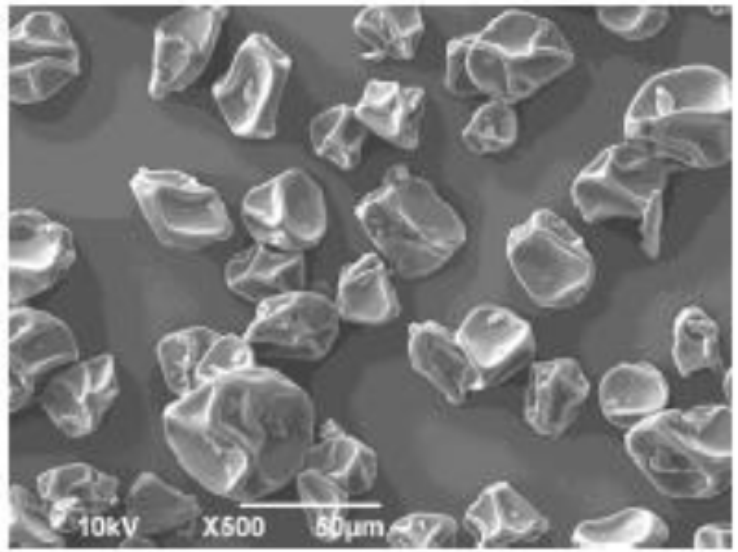
Loxapine Succinate / HPMC / Mannitol







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PK Data – Cynomolgus Monkeys

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IV and Oral comparators

- 35% Propylene Glycol was selected based on review of several products for intravenous administration:
  - Ativan Injection (lorazepam injection, USP) - (40% propylene glycol, 9% ethylene glycol),
  - Zemplar (paricalcitol) injection (30%, propylene glycol, 20% alcohol),
  - Amidate™ (etomidate) injection, USP (35% propylene glycol)
- Formulated at 3 mg / ml for either oral or IV administration
  - Solution stability and resuspension homogeneity - acceptable

Table 6. Solution Stability and Resuspension Homogeneity Results - 35% Propylene Glycol

	Initial Recovery (60-minute Avg)	Recovery after 24 hours at 25°C	Recover after 48 hours at 25°C
Average	99.5%	98.7%	99.0%
RSD	0.2%	0.8%	0.1%
Change	N/A	-0.8%	-0.5%

  - Filter qualification study - acceptable

Table 5. Filter Qualification Results

3 mg/mL loxapine in 35% propylene glycol	Loxapine Concentration
Before filtration (average of 60-minute time point)	3.04 mg/mL
After filtration	3.04 mg/mL

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Bioanalytical Method / Dosing NHPs

Alturas Analytics, Inc.
The LC-MS Experts

2. Extraction Method

1. Add 25.0 µL of working solution to 475 µL of plasma.
2. Add 50.0 µL of sample, standard, or QC.
3. Add 25.0 µL internal standard working solution (10.0 ng/mL Lox/8-OH; 5.00 ng/mL amox/7-OH) in dimethylformamide.
4. Precipitate with 250 µL acetonitrile + 0.1% formic acid.
5. Transfer 100 µL to a clean plate.
6. Reconstitute with 100 µL water + 0.1% formic acid.

3. Equipment

Mass Spectrometer: SCIEX API-6500
HPLC Pumps: Schimadzu LC-40D
HPLC Autosampler: Shimadzu SIL 40C

4. HPLC Conditions

Mobile Phase A:	Acetonitrile + 0.1% formic acid
Mobile Phase B:	Water + 0.1% formic acid
Rinse Solvent:	1:1 water:methanol
Column:	C18
Flow Rate:	0.600 mL/min
Injection Volume:	1.00 µL

Time	Module	Events	Parameter
2.0	Pumps	Pump B Conc.	22.0
3.5	Pumps	Pump B Conc.	35.0
4.0	Pumps	Pump B Conc.	95.0
4.5	Pumps	Pump B Conc.	95.0
4.8	Pumps	Pump B Conc.	35.0
5.5	Pumps	Pump B Conc.	35.0
5.9	System Controller	STOP	8.0

LOVELACE BIOMEDICAL

Formulation	Route	Animals
35% Propylene Glycol	Oral	4 NHP males
35% Propylene Glycol	IV	4 NHP males
Loxapine Alone	Nasal	4 NHP males
Loxapine / HPMC / Mannitol	Nasal	4 NHP males
Loxapine / HPMC / Mannitol / $CaCl_2$	Nasal	4 NHP males

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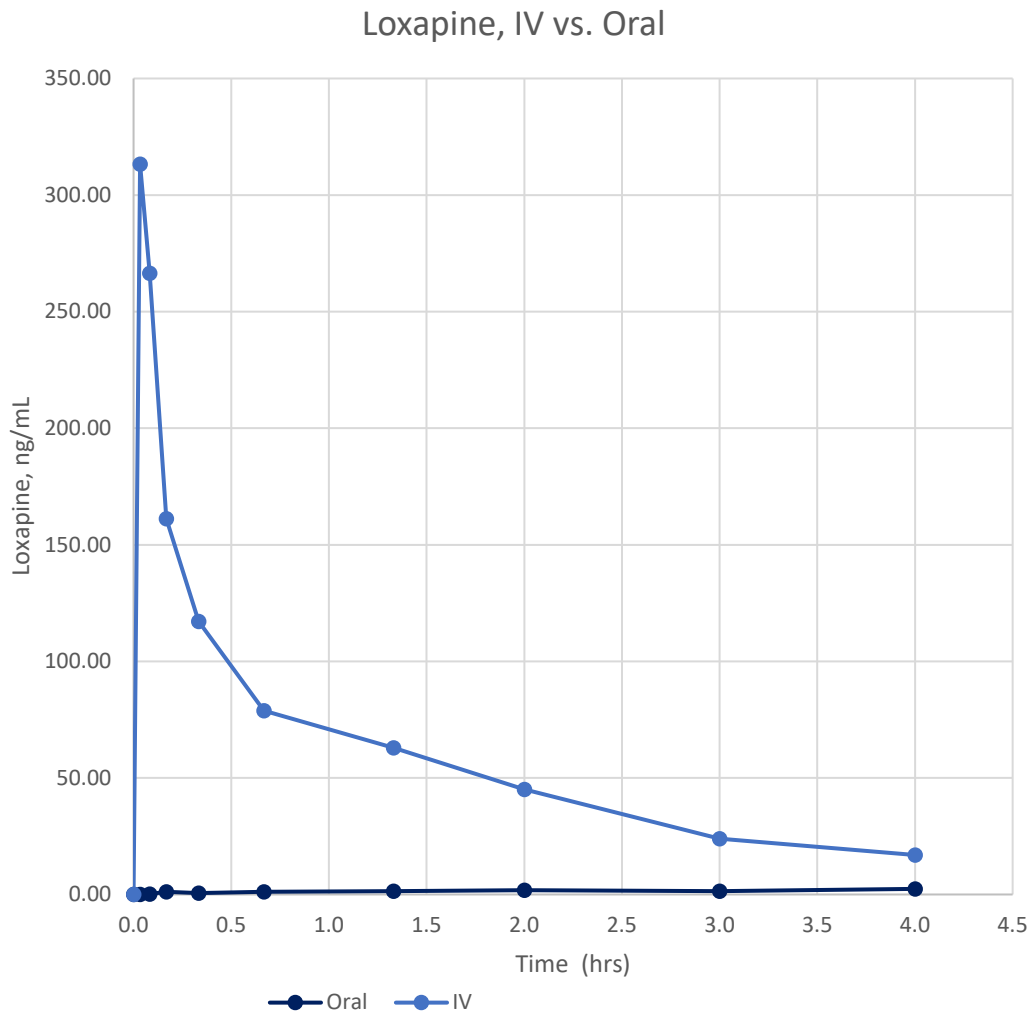
IV versus Oral



Parameter	Intravenous (IV)	Oral
Cmax (ng/mL)	364.0	3.3
AUC (4 hr, ng/mL*h)	231.5	5.9
AUC (2 hr, ng/mL*h)	176.6	2.4
AUC (20 min, ng/mL*h)	60.7	0.2
Tmax (min)	2.7	112.5
Tlag (min)	0	2.0
Kel (h-1)	0.49	ND
T½ (h)	1.43	ND

Very poor oral absorption

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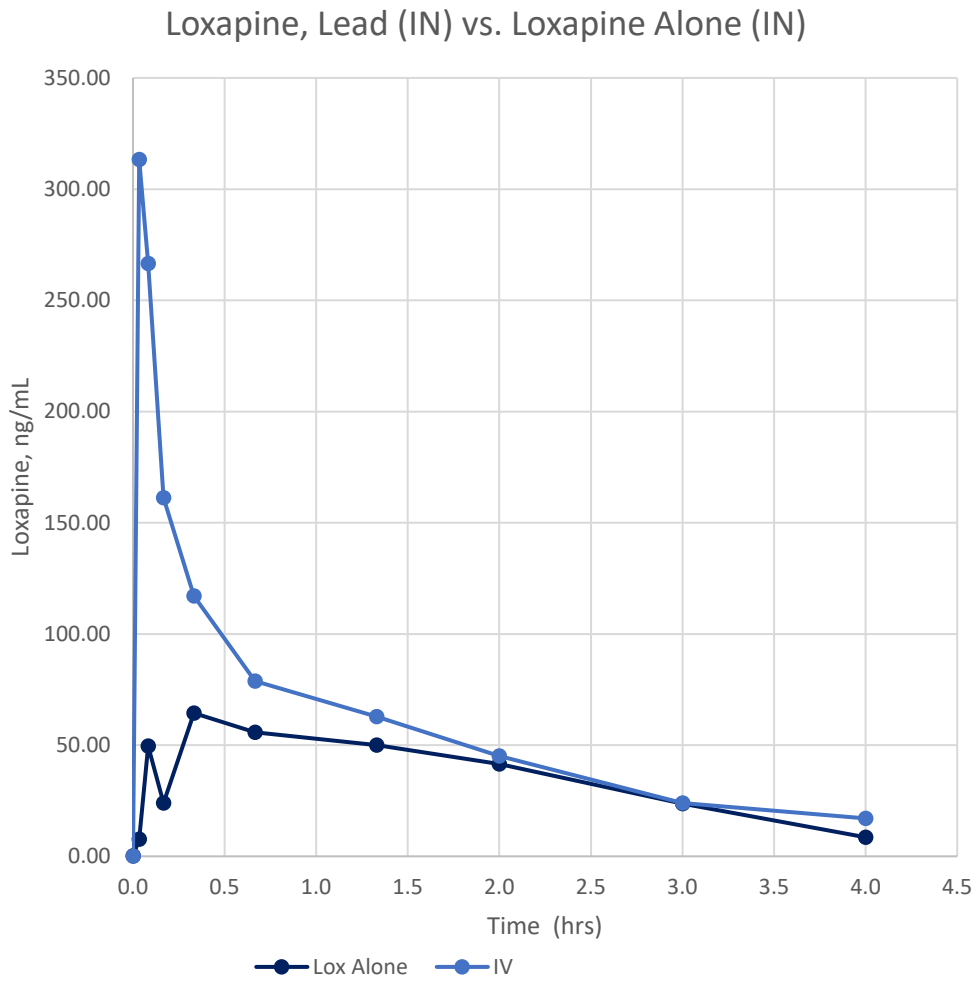
IV versus Spray Dried Loxapine Alone



Parameter	Intravenous (IV)	Loxapine alone
Cmax (ng/mL)	364.0	75.5
AUC (4 hr, ng/mL*h)	231.5	146.5
AUC (2 hr, ng/mL*h)	176.6	97.7
AUC (20 min, ng/mL*h)	60.7	12.0
Tmax (min)	2.7	39.9
Tlag (min)	0	0.0
Kel (h-1)	0.49	0.55
T½ (h)	1.43	1.25

55% AUC_{2hr} compared to IV

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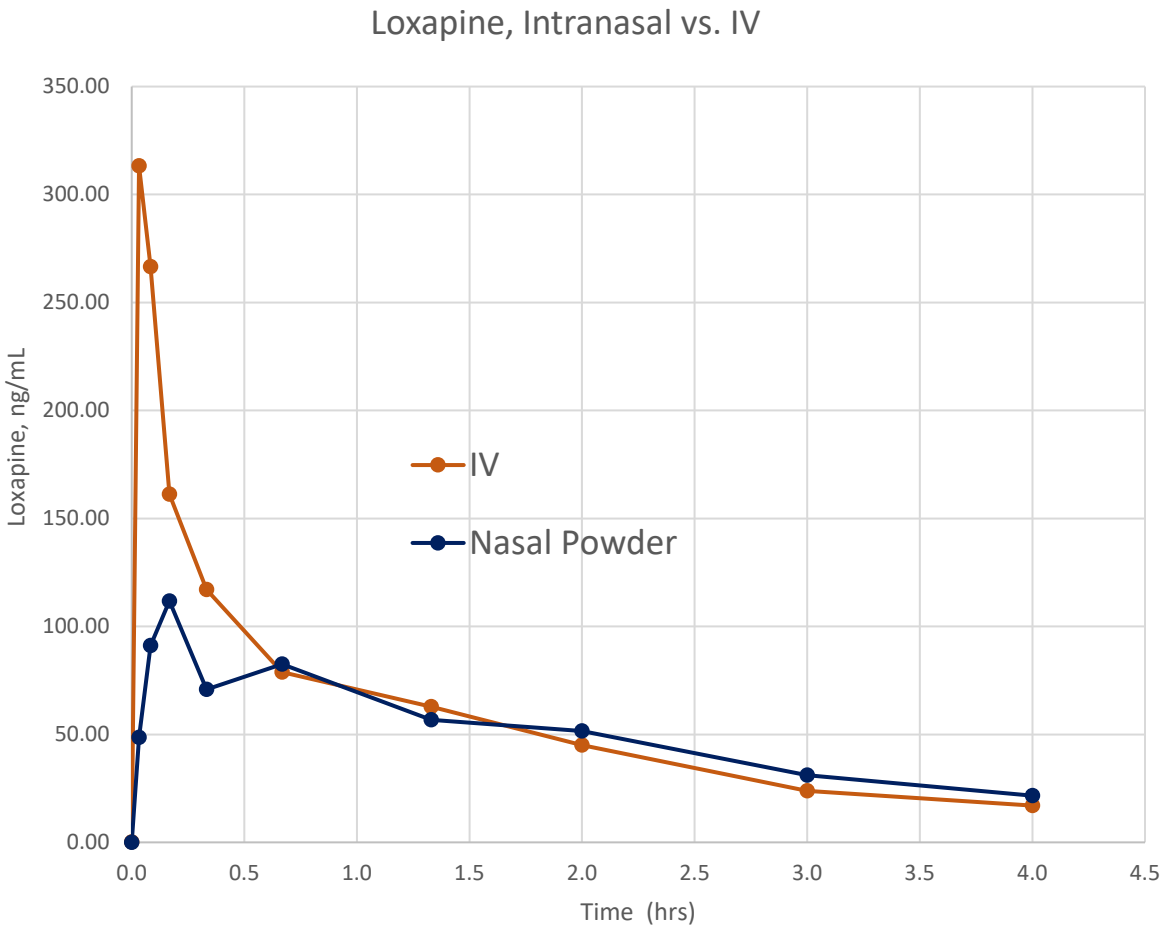
IV versus Spray Dried Loxapine / HPMC / Mannitol



Parameter	Intravenous (IV)	HPMC/Mannitol
Cmax (ng/mL)	364.0	140.4
AUC (4 hr, ng/mL*h)	231.5	203.9
AUC (2 hr, ng/mL*h)	176.6	136.1
AUC (20 min, ng/mL*h)	60.7	28.0
Tmax (min)	2.7	8.8
Tlag (min)	0	2.0
Kel (h-1)	0.49	0.40
T½ (h)	1.43	1.75

77% AUC_{2hr} compared to IV

- Matches IV after 30 minutes
- IV in NHP – wider peak than Adasuve in humans
  - See next slide

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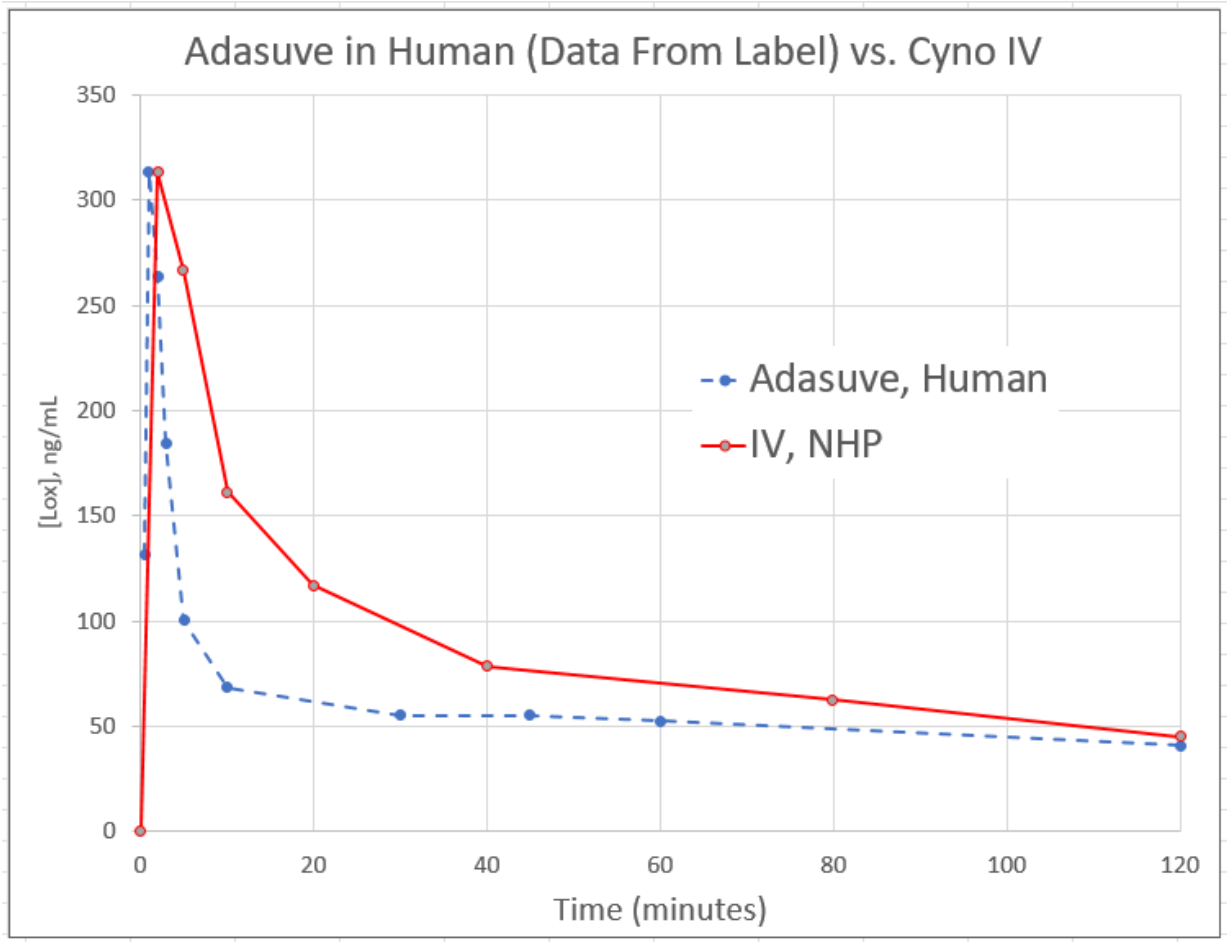
How well does the NHP IV model the Adasuve in Humans?



Adasuve results in a much sharper peak in humans than IV does in NHPs

- Could mean the Lox/HPMC/Man formulation would be even closer to Adasuve in humans

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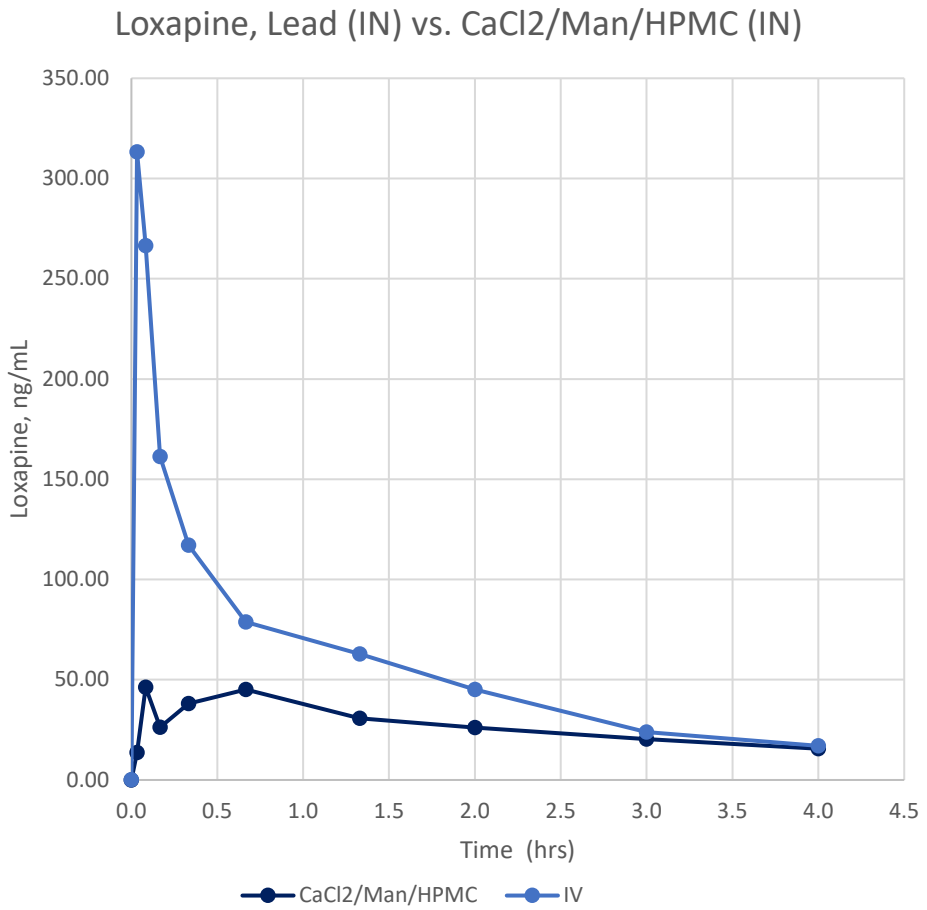
IV versus Spray Dried Loxapine / HPMC / Mannitol / $CaCl_2$



Parameter	Intravenous (IV)	HPMC/Mannitol (High Loxapine)
Cmax (ng/mL)	364.0	94.8
AUC (4 hr, ng/mL*h)	231.5	160.7
AUC (2 hr, ng/mL*h)	176.6	103.3
AUC (20 min, ng/mL*h)	60.7	19.2
Tmax (min)	2.7	40.0
Tlag (min)	0	2.0
Kel (h-1)	0.49	0.29
T½ (h)	1.43	2.39

58% AUC_{2hr} compared to IV

- Better dissolution
- Lower bioavailability

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Next Steps

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Human PK study

- Ideally, 3-way cross over:
  - Adasuve (10 mg),
  - Loxapine nasal powder (10 mg)
  - Loxapine nasal powder (15 mg)
- Measure $AUC_{2hr,}$ AUC_{inf}
- Interpolate to determine bioequivalent dose
  - Conduct full BE study
- CMC and toxicology data available

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