ASCPT

FROM MOLECULE TO PATIENT

ASCPT 2019 ANNUAL MEETING

Nasal PK Study of Abuse-Deterrent Opioid Products Following Insufflation of Physically Manipulated Products

Bradley D. Vince, D.O.

President & Medical Director, Altasciences/Vince & Associates

This study was funded through FDA contract HHSF223201510138C to Vince and Associates Clinical Research Inc. Views expressed in this poster do not necessarily reflect the official policies of the Department of Health and Human Services, nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

Agenda

- Clinical Study Design
- Safety Results
- Bioanalytical Method
- Pharmacokinetic Results
- Conclusions
- Additional Safety Information
- Question & Answer

FROM MOLECULE TO PATIENT

Study Design and Objectives

Study Objectives

Objectives: The purpose of this study was to investigate factors (particle size and formulation) that influence bioavailability of milled opioid drug products following intranasal insufflation.

The specific objectives of this study were to:

- To assess the pharmacokinetics (PK) of milled oxycodone HCl extended-release (ER) tablets compared to milled immediate-release (IR) oxycodone HCl tablets following intranasal insufflation in recreational opioid users.
- To assess the effects of ratio of excipient to active pharmaceutical ingredient (oxycodone HCl) on nasal bioavailability.
- To assess the safety of milled oxycodone HCl ER compared to milled oxycodone IR following intranasal insufflation in recreational opioid users, when administered under a naltrexone block.

Study Design

- **Study Design:** Single center, randomized, open-label, single dose, 4-sequence, 4-period, 4-treatment crossover design
- **Treatments**
  - Finely milled oxycodone ER 30 mg tablets (Treatment-A)
  - Coarsely milled oxycodone ER 30 mg tablets (Treatment-B)
  - Finely milled oxycodone ER 80 mg tablets - administered as a 30 mg dose (Treatment-C)
  - Finely milled oxycodone IR 30 mg tablets (Treatment-D)
- **Particles sizes**
  - Finely milled - 10 to 500 µm
  - Coarsely milled - 500 to 1,000 µm

Study Design (cont.)

- **Subjects**
  - Male and female opioid users with a history of recreational intranasal drug use, otherwise healthy
    - Recreational opioid use defined as at least 10 recreational uses in their lifetime **AND** at least one use within 12 weeks prior to Screening
  - History of nasal insufflation experience with recreational drugs on at least 4 occasions in 12 months prior to Screening
  - Excluded if moderate to severe substance use disorder w/in previous 12 months (defined by DSM-V, 5th edition)
  - Excluded if physically dependent on opioids as demonstrated by a failed Naloxone Challenge

Study Design (cont.)

- **Naltrexone block**
  - All subjects were administered naltrexone before and after oxycodone administration
- **Pharmacokinetic sampling**
  - Serial blood samples collected pre-dose and until 48 hours after each administration
- **Washout**
  - 72 hours between administrations

Study Design (cont.)

- Subjects confined to the clinic one day prior to 1st dose until approx. 48 hrs after last dose
- Screening Period: Day -28 to Day -1
- Day -1: Admission to Clinic
- Day 1: 1st Dose
- Day 4: 2nd Dose
- Day 7: 3rd Dose
- Day 10: 4th Dose
- Day 12: Discharge
- Follow-Up Call: Approximately 48-72 hrs following clinic discharge

FROM MOLECULE TO PATIENT

Safety Results

Subject Disposition

Category		Overall
Subjects included, N		41
Number of Subjects in Each Population [n(%)]	Safety Population	41 (100)
	PK & Statistical Population	36 (88)
Subject discontinued before end of study [n(%)]	Yes	8 (20)
	No	33 (80)

- A total of 41 subjects were included in this study.

- After randomization, 37 subjects received Treatment A at least once, 37 subjects received Treatment B at least once, 35 subjects received Treatment C at least once, and 36 subjects received Treatment D at least once.

Safety Results

- Overall, 78% of subjects experienced 114 TEAEs in the study
- There were no deaths, SAEs, or AESIs in the study.
- The overall incidence and number of TEAEs was similar with finely milled oxycodone ER 30 mg and 80 mg tablets, slightly lower with oxycodone IR and lowest with coarsely milled oxycodone ER

Safety Results (cont.)

- Five subjects (12.2%) withdrew from the study due to mild TEAEs that were considered expected and at least possibly related to study drug:
  - Blood pressure increased (oxycodone IR)
  - Blood bilirubin increased (Coarsely milled oxycodone ER)
  - Decreased appetite, nausea, vomiting and headache (Finely milled 80 mg oxycodone ER)
  - Vomiting (Coarsely milled oxycodone ER)
  - Irritability (Finely milled oxycodone ER)

- Five subjects required concomitant medications (ibuprofen or acetaminophen) to treat TEAEs during the study, the majority of which were expected and considered at least possibly related to study drug:
  - Finely milled oxycodone ER : Headache
  - Coarsely milled oxycodone ER : oropharyngeal pain and neck pain (not related); 3 x headache; dental caries (not related)
  - oxycodone IR : 2 x headache (1 not related)

FROM MOLECULE TO PATIENT

Bioanalytical Method

Bioanalytical Method

- Measurement of oxycodone plasma concentration
- The experimental samples were assayed for oxycodone at the bioanalytical facility of Altasciences.
- **Validated Method**: HPLC method with MS/MS detection.
- **Range of detection** : 0.200 ng/mL and 100.000 ng/mL.
- **Extraction type** : liquid-liquid extraction.
- **Matrix and Anticoagulant**: human plasma in K_2EDTA.
- **Internal Standard(IS)** : Oxycodone-D_6.

Bioanalytical Method

- **The Incurred Sample Reproducibility:** The evaluation was successfully assessed at 99.4 % of reproducibility

Total of samples received	**3067**
Total of samples successfully assayed	3067
Samples re-assayed as ISR	312
Samples have met the percent difference criterion of ≤20.0%	310

- A Bioanalytical Plan containing information about the conduct of the bioanalytical portion of the study was completed and approved prior to sample analysis.

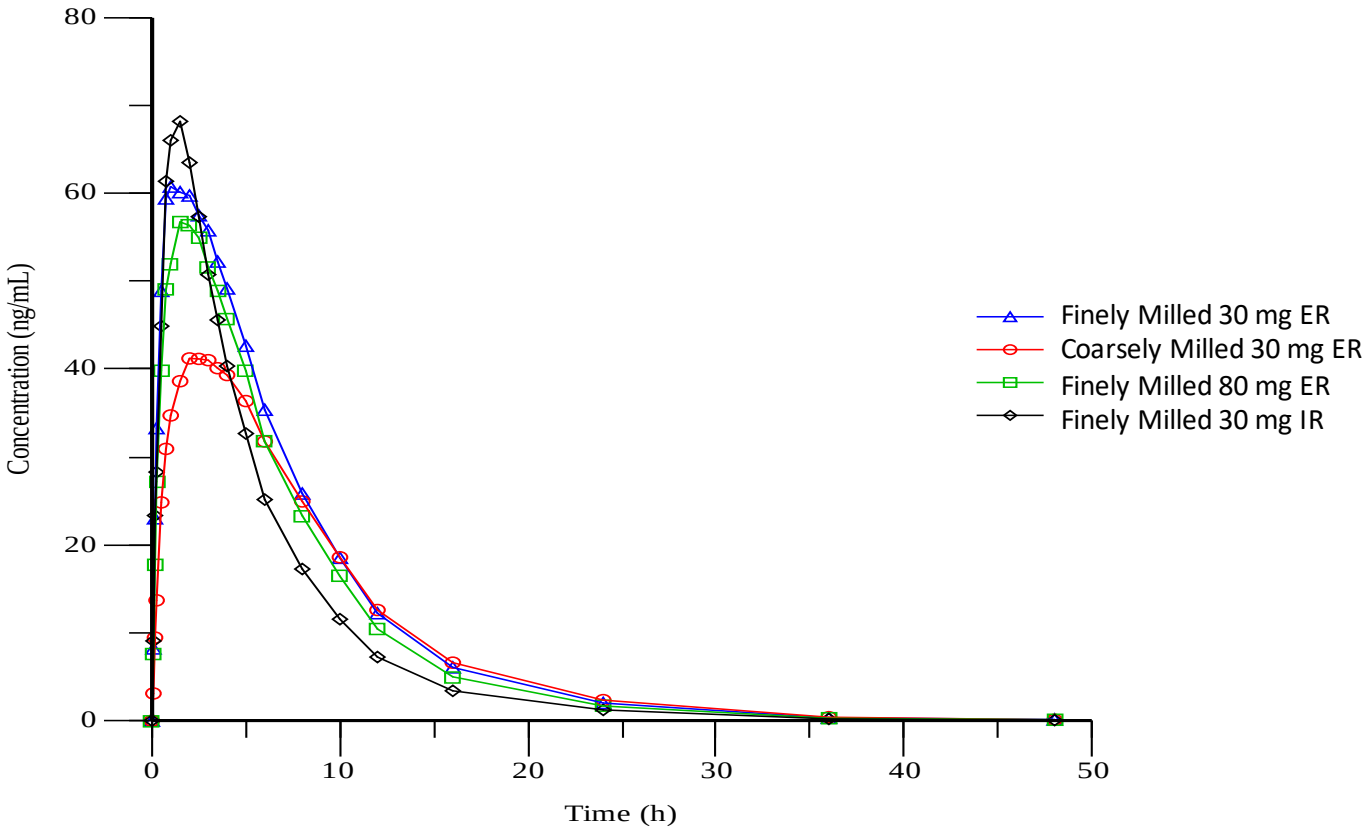
FROM MOLECULE TO PATIENT

Pharmacokinetic Results

Treatment Compliance for PK Population

- Compliance status was listed as “complete” for majority of subjects. Two subjects had “incomplete” compliance status, both for insufflation of coarsely milled oxycodone ER:
  - Subject 1080 sneezed during dosing, in addition to there being a slight amount left on the catch paper at 2 minutes, and slight residue in both nares.
  - Subject 1047 did not insufflate all of the IP in 3 minutes, and a small amount discharged from the subject’s nose and was returned to the bottle. There was also some residue in the subject’s nares. Difference in pre- and post-dose weights (i.e., drug insufflated) within range of other subjects.
- These subjects were not excluded from the Pharmacokinetic Population as they gave evaluable data for at least one comparison.

Mean Plasma Concentrations of Oxycodone



Pharmacokinetic Results

Effect of Abuse-Deterrent Formulation – Oxycodone ER 30 mg or 80 mg vs. Oxycodone IR

- **Finely Milled oxycodone ER versus Finely Milled oxycodone IR:**
  - Peak exposure was slightly lower with finely milled oxycodone ER (64.1 versus 78.0 ng/mL; lower bound of ratio 75.2%).
  - Exposure over 30 minutes (12.9 versus 11.3 ng*h/mL; upper bound of ratio 133.8%) and total exposure (488.1 versus 400.5 ng*h/mL; upper bound of ratio 129.2%) were higher with finely milled oxycodone ER
  - Oxycodone IR versus oxycodone ER did not pass the non-inferiority test for peak exposure (upper bound of ratio 135.5%) but was non-inferior for other pharmacokinetic parameters.

Pharmacokinetic Results (cont.)

- **Coarsely Milled oxycodone ER versus Finely Milled oxycodone IR:**
  - Peak exposure (46.0 versus 77.8 ng/mL; lower bound of ratio 54.3%) and exposure up to 4 hours (136.2 versus 204.8 ng/mL; lower bound of ratio 61.3%) were lower with coarsely milled oxycodone ER
  - Bioequivalence was observed for total exposure

- **Finely Milled oxycodone ER (80 mg) versus Finely Milled oxycodone IR:**
  - Finely milled oxycodone ER – 80 mg tablet had a lower peak exposure (60.0 versus 78.3 ng/mL; lower bound of ratio 70.8%) and exposure in the first hour (34.2 versus 39.5 ng*h/mL; lower bound of ratio 77.6%).
  - Bioequivalence was observed for other parameters.

Pharmacokinetic Results (cont.)

Effect of Particle Size – Oxycodone ER Finely Milled vs. Coarsely Milled

- **Finely milled oxycodone ER versus coarsely milled oxycodone ER** Finely milled oxycodone ER has higher peak exposure (64.8 versus 45.6 ng/mL; upper bound of ratio 154.8%) and overall exposure (492.2 versus 415.1 ng*h/mL; upper bound of ratio 126%) compared with coarsely milled oxycodone ER . These differences were seen across all PK parameters.

  - Higher exposure to oxycodone when oxycodone ER is finely milled compared to coarse particle size was confirmed in the non-inferiority analysis (upper bound ranges from 126.1% to 280.0%)

Pharmacokinetic Results (cont.)

Effect of Excipient to API Ratio

- **Oxycodone ER (80 mg vs. 30 mg) Tablets**
  - The exposure to 1 hour (34.4 versus 40.0 ng*h/mL; lower bound of ratio 78.4%) was lower for 80 mg. However, the peak exposure and total exposure were bioequivalent between the 30 mg and 80 mg tablets.
  - In the non-inferiority analysis of 80 mg versus 30 mg, 80 mg tablets were deemed to be non-inferior to 30 mg tablets on all PK parameters (upper bound never exceeded 102.0%)

Conclusions

Conclusions

- The study showed that finely milled non-abuse deterrent oxycodone IR did not pass the non-inferiority test for Cmax when compared with finely milled oxycodone ER treatments
- The study demonstrated a significant effect of particle size on the bioavailability of oxycodone ER, when administered intranasally.
- The study demonstrated there was not a significant effect of excipient to API ratio on the bioavailability of oxycodone ER, when administered intranasally and finely milled (106-500 micron).
- The intranasal oxycodone treatments, administered under naltrexone block, were safe and relatively well-tolerated in non-dependent recreational opioid users.

Acknowledgement

- Debra Kelsh, MD – Principal Investigator, Altasciences/Vince & Associates
- U.S. FDA OGD Collaborative Teams
- Tonglei Le, PhD - Purdue University Department of Industrial and Physical Pharmacy
- Purdue GMP Center

FROM MOLECULE TO PATIENT

Additional Safety Information

Overview of Adverse Events

	30 mg Finely milled oxycodone ER - 30 mg tablet (Treatment-A) N=37	30 mg Coarsely milled oxycodone ER - 30 mg tablet (Treatment-B) N=37	30 mg Finely milled oxycodone ER - 80 mg tablet (Treatment-C) N=35	30 mg Finely milled oxycodone IR - 30 mg tablet (Treatment-D) N=36	Overall N=41
Subjects with ≥1 TEAE, n (%) [# of TEAEs]	17 (45.9) [37]	10 (27.0) [16]	17 (48.6) [39]	14 (38.9) [22]	32 (78.0) [114]
Subjects with ≥1 drug-related TEAE, n (%)	16 (43.2)	9 (24.3)	16 (45.7)	13 (36.1)	31 (75.6)
TEAE relationship, n (%)[b]					
Related	34 (91.9)	12 (75.0)	37 (94.9)	19 (86.4)	102 (89.5)
TEAE severity, n (%)					
Mild	35 (94.6)	14 (87.5)	39 (100.0)	21 (95.5)	109 (95.6)
Moderate	2 (5.4)	2 (12.5)	0	1 (4.5)	5 (4.4)
Severe	0	0	0	0	0
Deaths, SAEs or AESIs, n	0	0	0	0	0
Subject withdrawal due to TEAE, n (%)	1 (2.7)	2 (5.4)	1 (2.9)	1 (2.8)	5 (12.2)

- 78% of subjects experienced 114 TEAEs.
- No deaths, SAEs, or AESIs; 5 subjects (12.2%) withdrew from the study due to TEAEs.
- Majority of TEAEs considered related to study drug (89.5%) and mild in severity (95.6%).
- Overall incidence/number of TEAEs similar with finely milled oxycodone ER – 30 mg and 80 mg tablets (Treatment-A and Treatment-C) (45.9% and 48.6%, respectively), slightly lower with oxycodone IR (Treatment D) (38.9%) and lowest with coarsely milled oxycodone ER (Treatment-B) (27.0%).
- Patterns were similar with drug-related TEAEs

Summary of TEAEs with Incidence >5% in any Treatment at Onset

MedDRA System Organ Class Preferred Term	30 mg Finely milled oxycodone ER - 30 mg tablet (Treatment-A) N=37	30 mg Coarsely milled oxycodone ER - 30 mg tablet (Treatment-B) N=37	30 mg Finely milled oxycodone ER - 80 mg tablet (Treatment-C) N=35	30 mg Finely milled oxycodone IR - 30 mg tablet) (Treatment-D) N=36
Subjects with ≥1 TEAE	**17 (45.9)**	**10 (27.0)**	**17 (48.6)**	**14 (38.9)**
Respiratory, thoracic and mediastinal disorders	**8 (21.6)**	**2 (5.4)**	**12 (34.3)**	**3 (8.3)**
Rhinorrhoea	5 (13.5)	0	6 (17.1)	0
Nasal Discomfort	2 (5.4)	0	4 (11.4)	0
Nasal Congestion	1 (2.7)	0	2 (5.7)	1 (2.8)
Nervous system disorders	**7 (18.9)**	**4 (10.8)**	**6 (17.1)**	**7 (19.4)**
Headache	4 (10.8)	3 (8.1)	1 (2.9)	4 (11.1)
Somnolence	2 (5.4)	1 (2.7)	3 (8.6)	1 (2.8)
Dizziness	1 (2.7)	0	2 (5.7)	2 (5.6)
Psychiatric disorders	**4 (10.8)**	**3 (8.1)**	**5 (14.3)**	**6 (16.7)**
Euphoric Mood	3 (8.1)	1 (2.7)	3 (8.6)	4 (11.1)
Agitation	0	0	2 (5.7)	0
Gastrointestinal disorders	**2 (5.4)**	**2 (5.4)**	**3 (8.6)**	**2 (5.6)**
Nausea	1 (2.7)	0	2 (5.7)	2 (5.6)
Vomiting	1 (2.7)	1 (2.7)	2 (5.7)	0
General disorders and administration site conditions	**5 (13.5)**	**1 (2.7)**	**2 (5.7)**	**1 (2.8)**
Feeling Hot	3 (8.1)	0	2 (5.7)	0

- **Most common SOCs overall:**
- Respiratory, thoracic and mediastinal disorders, Nervous system disorders, Psychiatric disorders, Gastrointestinal disorders, General disorders and administration site conditions.
- **Most common individual TEAEs (>5%):**
- Treatment-A: rhinorrhoea, headache, euphoric mood, feeling hot, nasal discomfort, somnolence.
- Treatment-C: rhinorrhoea, nasal discomfort, nasal congestion, somnolence, euphoric mood, dizziness, agitation, nausea, vomiting, feeling hot.
- Treatment-D: headache, euphoric mood, dizziness, nausea
- Treatment-B: headache

Q&A