From: James G King Jr
To: Susan Larijani (Susan.Larijani@tevapharm.com); Shweta Shah
Sent: 6/26/2015 11:24:28 AM
Subject: IR Hydrocodone Kick-off Slides
Attachments: Kickoff All Hands_Final.pptx

Dierks Exhibit
9
10/13/21 - ctm

Susan,

Attached is the slide deck from the IR hydrocodone kick-off meeting Wednesday.

Regards,
Jim

James G King Jr., Ph.D.
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North America Medical Affairs, Global Specialty Medicines
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PLAINTIFF TRIAL EXHIBIT
P-22527_00001

File Provided Natively

IR Hydrocodone Commercial Kickoff All Hands Meeting

June 24th, 2015

Agenda

Section	Presenter	Time
Breakfast		8:00-8:30
Welcome and Introduction	Heather Schoenly	8:30-8:45
Project Overview	Dorit Mimrod	8:45-9:00
CIMA Technology/CMC	Derek Moe	9:00-9:30
Product Overview	Maciej Gasior	9:30-9:45
Break		9:45-10:00
Clinical Pharmacology	Mary Bond	10:00-11:00
Phase III Studies	Maciej Gasior	11:00-11:30
Regulatory Affairs	Jennifer Pansch	11:30-12:00
Launch Governance	Heather Schoenly	12:00-12:10
Close	Jeff Dierks	12:10-12:15
Lunch		12:15-1:00

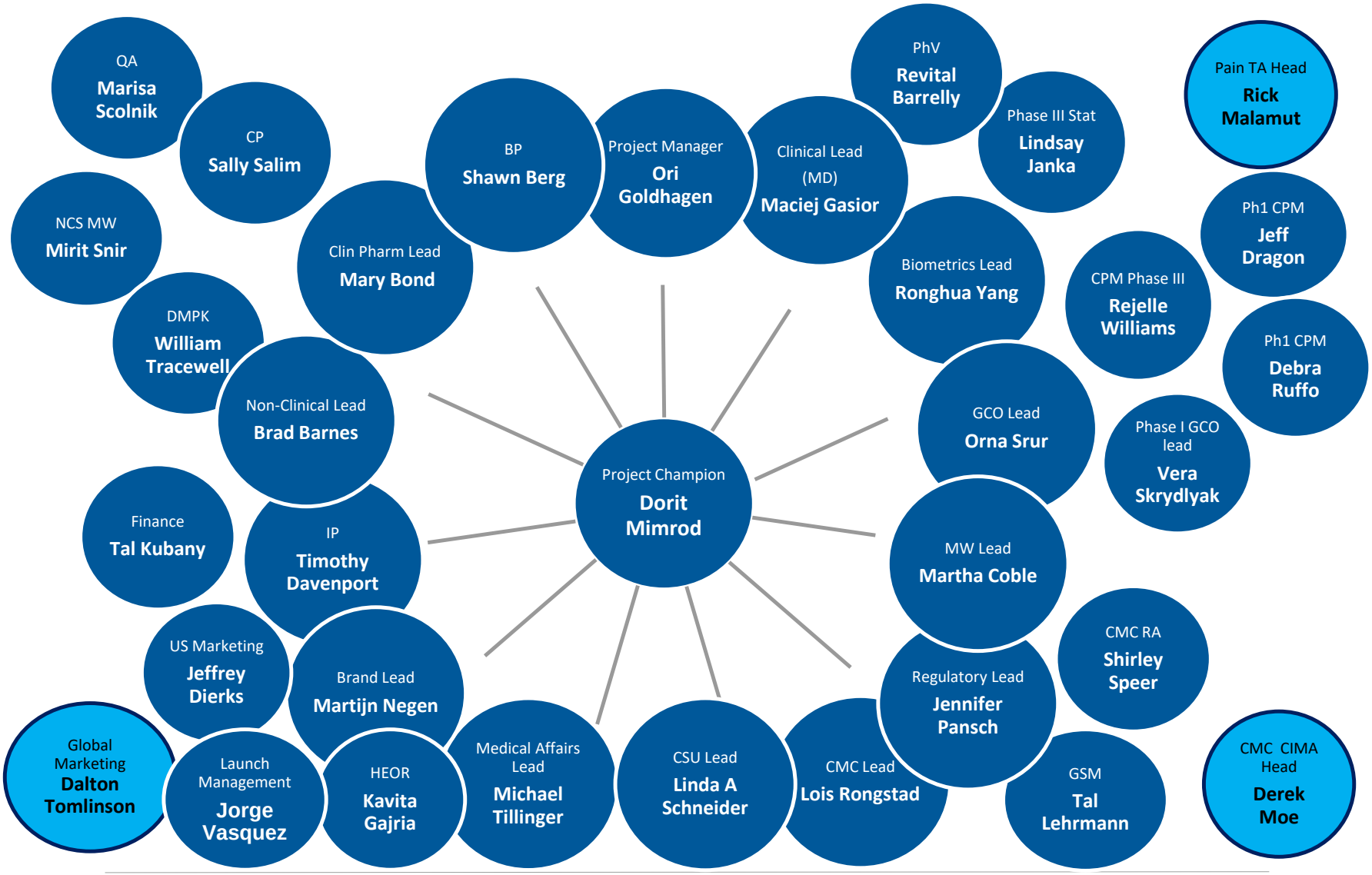
Objective

- Educate key stakeholders on IR hydro to prepare for the commercial launch in 2017

Project Overview

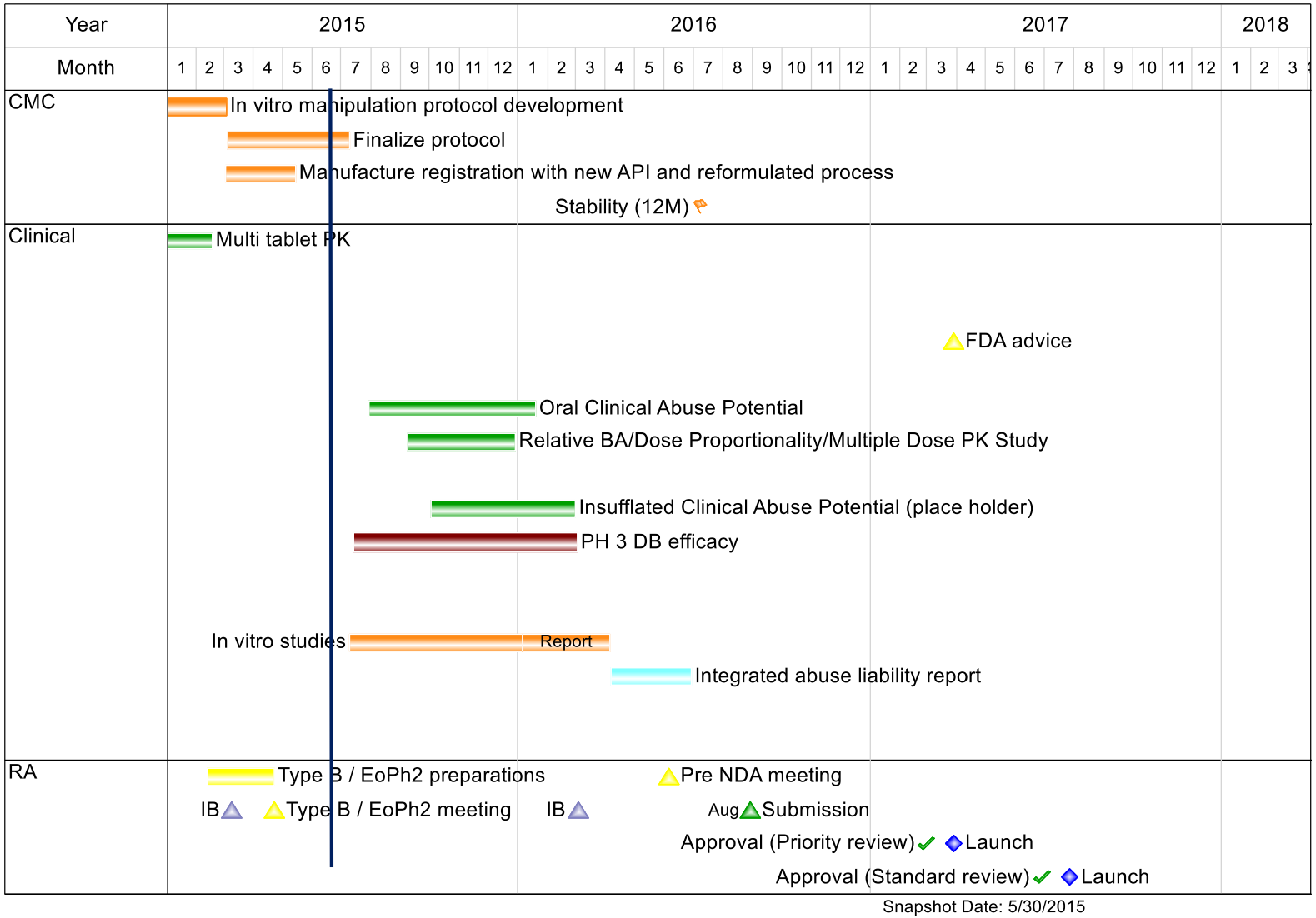
Dorit Mimrod, Ph.D.; Project Champion

Global Project Team



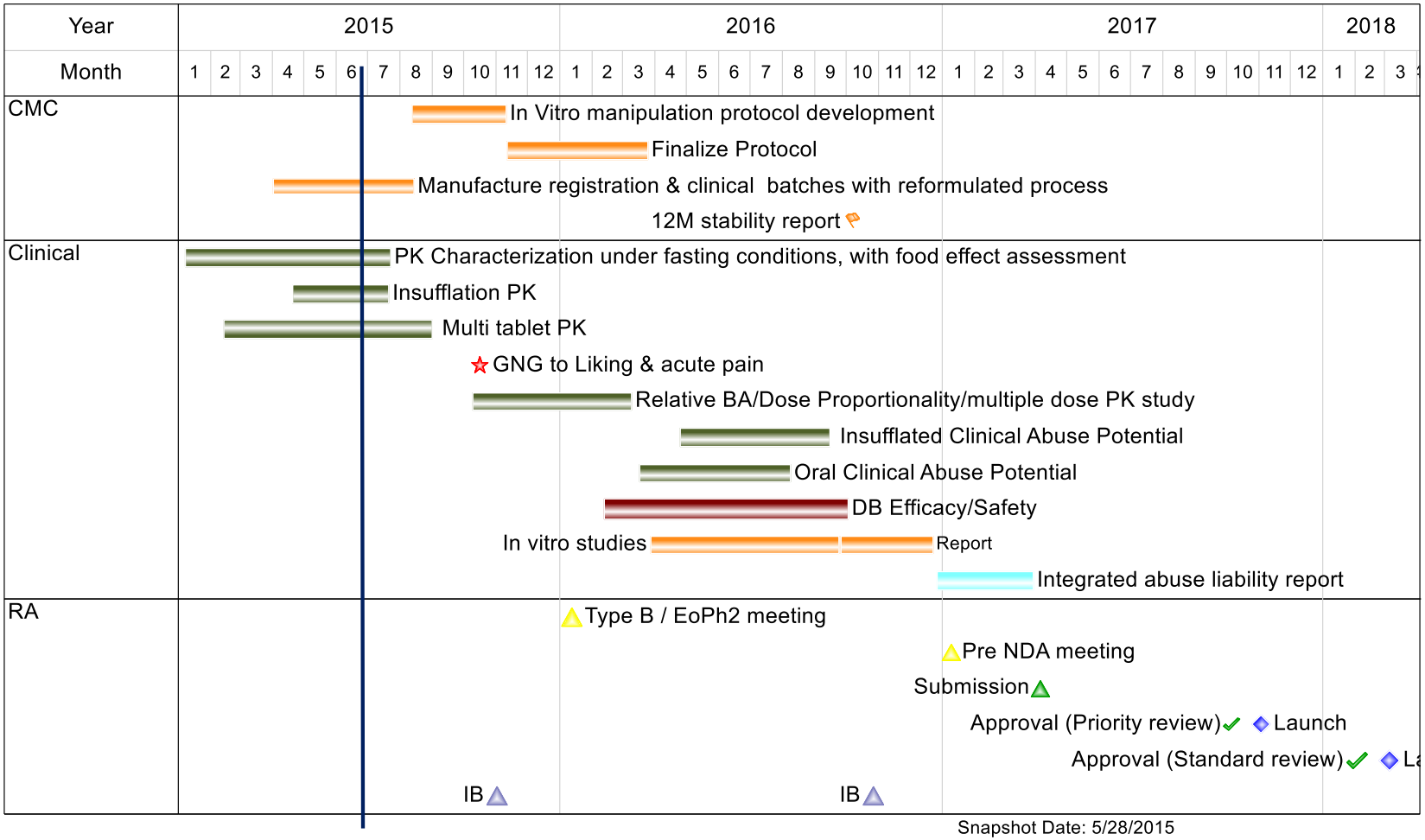
P-22527 _ 00007

TV-46763 Hydrocodone APAP IR - HLG



Snapshot Date: 5/30/2015

TV-46139 Oxycodone\APAP IR- HLG



CIMA Technology/CMC

Derek Moe

IR Abuse Deterrent OraGuard

- Properties:
  - Resistance to multiple tablet oral abuse/overdose
  - Crushed tablet resistant to snorting
  - Crushed tablet resistant to small volume extraction for IV abuse
  - Immediate release properties not affected by abuse deterrent attributes
  - Pain patients taking the product as prescribed will not be adversely affected by abuse deterrent features

Abuse Deterrent
Short-acting Hydrocodone + APAP

- Abuse deterrent Vicodin-like product for US market
- Utilize OraGuard™ platform tuned for immediate release
  - Gel-forming polymers
- Resist common abuse methods
  - Multiple tablet administration orally
  - Nasal insufflation
  - Extraction for IV
- 5, 7.5, and 10 mg strengths, all with 325 mg APAP

Abuse Deterrent
Short-acting Oxycodone + APAP

- Abuse deterrent Percocet-like product for US market
- Utilize OraGuard™ platform tuned for immediate release
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- Resist common abuse methods
  - Multiple tablet administration orally
  - Nasal insufflation
  - Extraction for IV
- 5, 7.5, and 10 mg strengths, all with 325 mg APAP

IR OraGuard: Formulation Approach

- When administered as directed
  - Tablet disintegrates rapidly in the stomach and the active ingredients are readily absorbed

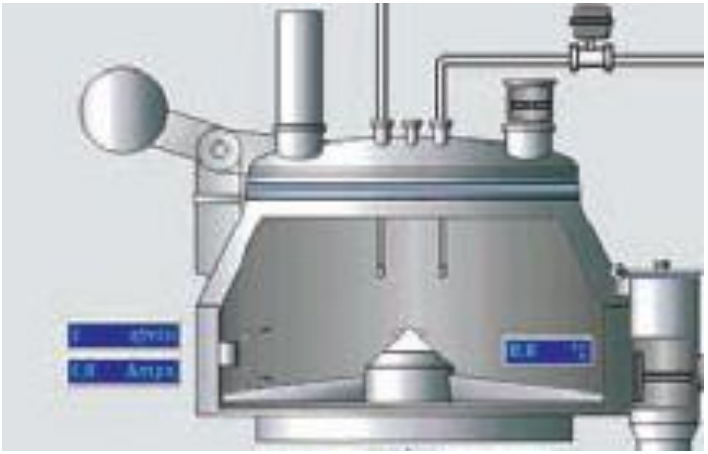
- When the tablets are crushed for nasal or IV abuse
  - Small volume of liquid not enough for tablet to disintegrate and release drug, gelling occurs instead
  - Crushing causes entrapped polymer to be released, causing gelling instead of drug release
  - pH sensitive polymers gel rapidly at neutral pH of nasal cavity or neutral pH of injection fluid

- When multiple tablets are taken orally
  - Tablets do not disintegrate, release profile converts from immediate release to extended release

OraGuard is a multilayer abuse deterrent approach

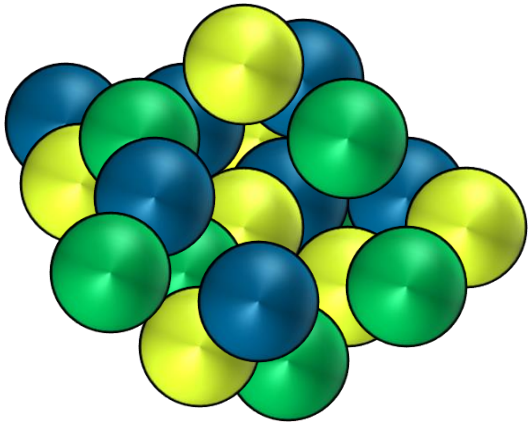
Step 1

Process



high shear granulation with rapidly gelling polymers

End product

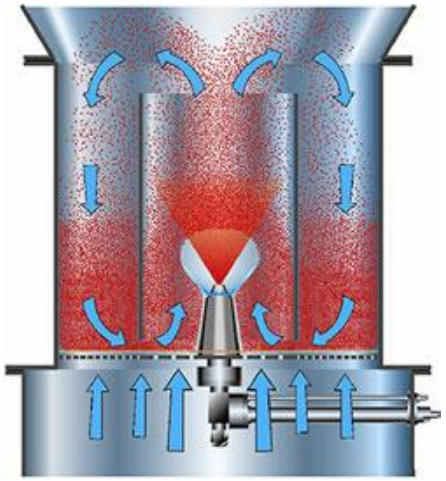


Inert core containing a mix of high viscosity polymers, rapidly gels when hydrated

OraGuard is a multilayer abuse deterrent approach

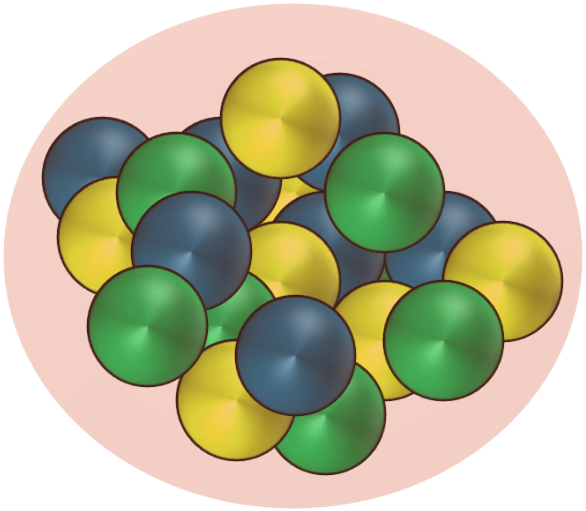
Step 2

Process



API is layered onto the polymer core

End product

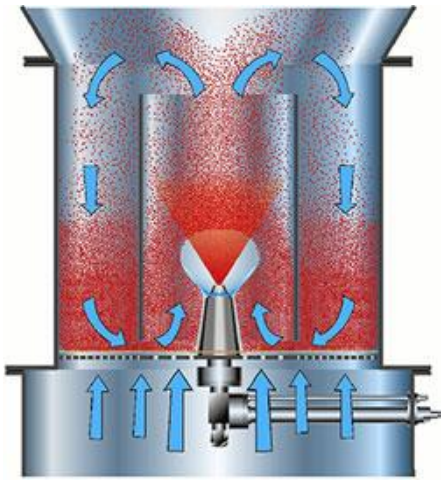


API coated polymer

OraGuard is a multilayer abuse deterrent approach

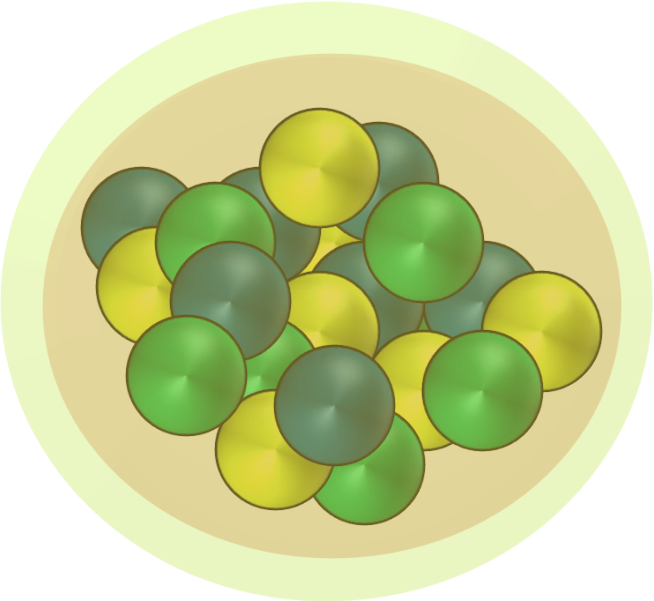
Step 3

Process



fluid bed coating with pH dependent polymer

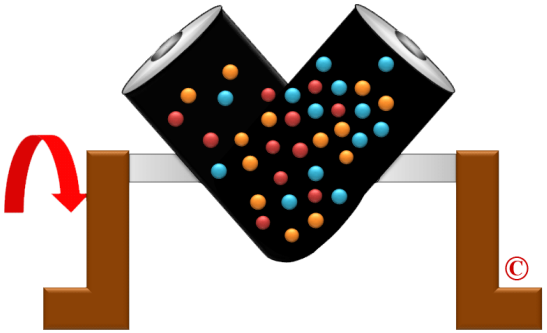
End product



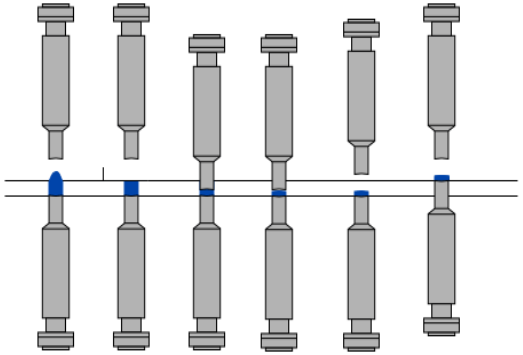
Prevents dissolution at neutral pH- nasal and IV

OraGuard is a multilayer abuse deterrent approach

Process



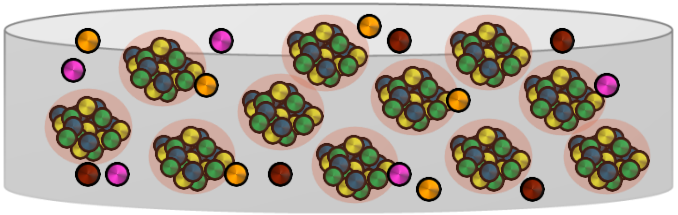
Blend with gel forming polymer and superdisintegrant



Compress into tablets

Step 4/5

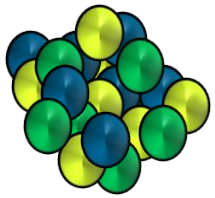
End product



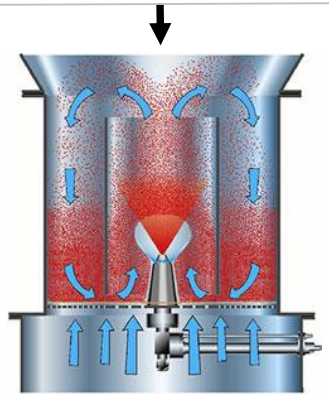
resist small volume solvent extraction and slow down release when multiple tablets are administered

Multilayer Abuse Deterrent Approach

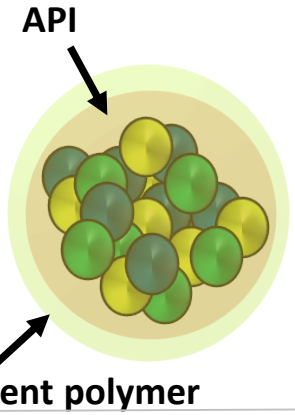
High shear granulation with rapidly gelling polymers



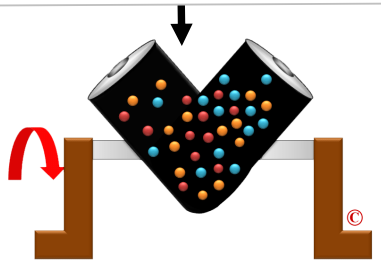
Inert core containing a mix of high viscosity polymers, rapidly gels when hydrated



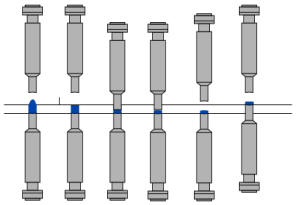
API is layered onto the polymer core, followed by another layer of pH dependent polymer



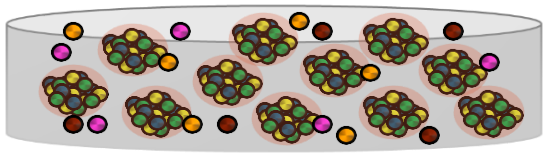
API coated polymer core that prevents dissolution at neutral pH (nasal and IV), slows release when crushed



Blend with gel forming polymer and superdisintegrant



Compress into tablets



Resists small volume solvent extraction and slows down release when multiple tablets are orally administered

How does one measure abuse deterrent properties?

- *In vitro* studies are designed to assess the robustness of the formulation against techniques, methods, and practices known to be used for abuse
  - Measures vulnerability of the dosage form

- *In vivo* liking studies are designed to assess the likeability of a compromised formulation in a group of calibrated recreational drug users
  - Measures desirability of the dosage form

FDA guidance April 2015 on AD Opioids

- 4 methods to characterize abuse deterrent properties
  - Laboratory-based in vitro manipulation and extraction studies (Category 1)
  - Pharmacokinetic studies (Category 2)
  - Clinical abuse potential studies (Category 3)
  - Analyze post-marketing data to assess the impact of an abuse-deterrent formulation on actual abuse (Category 4)

FDA guidance April 2015 on AD Opioids

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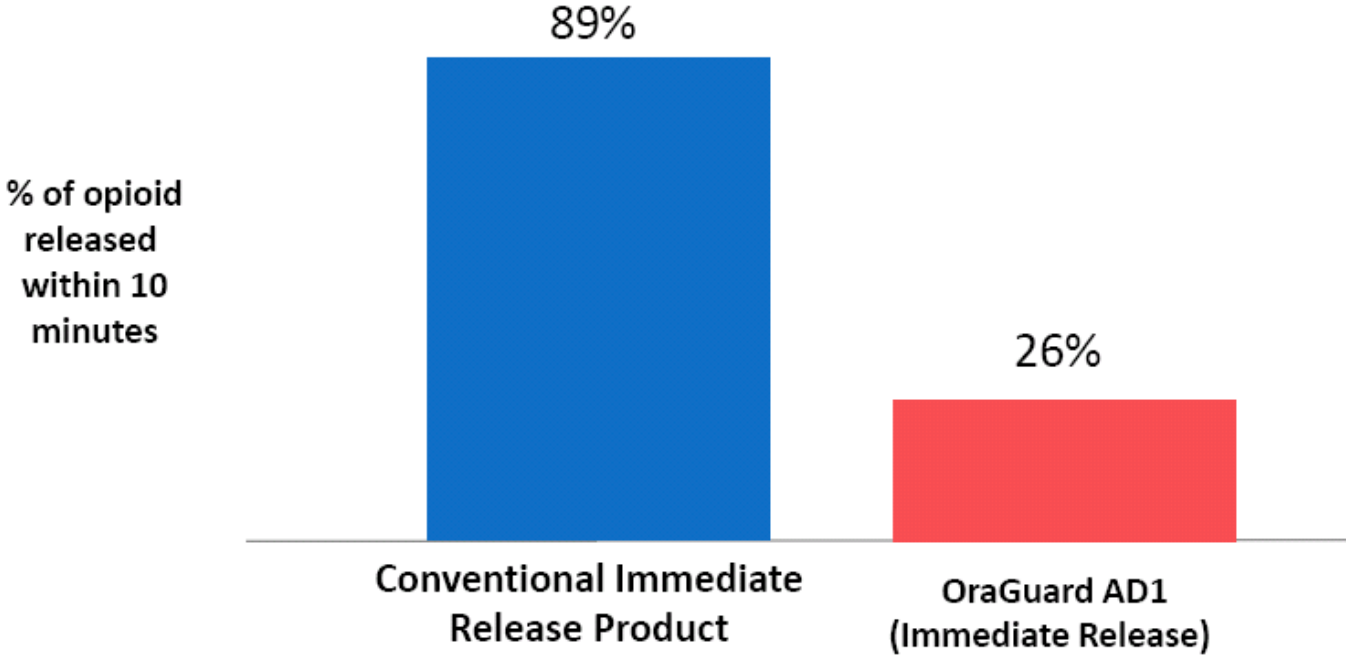
Oraguard protects against crushing and snorting

In-vitro crushing and snorting experiment

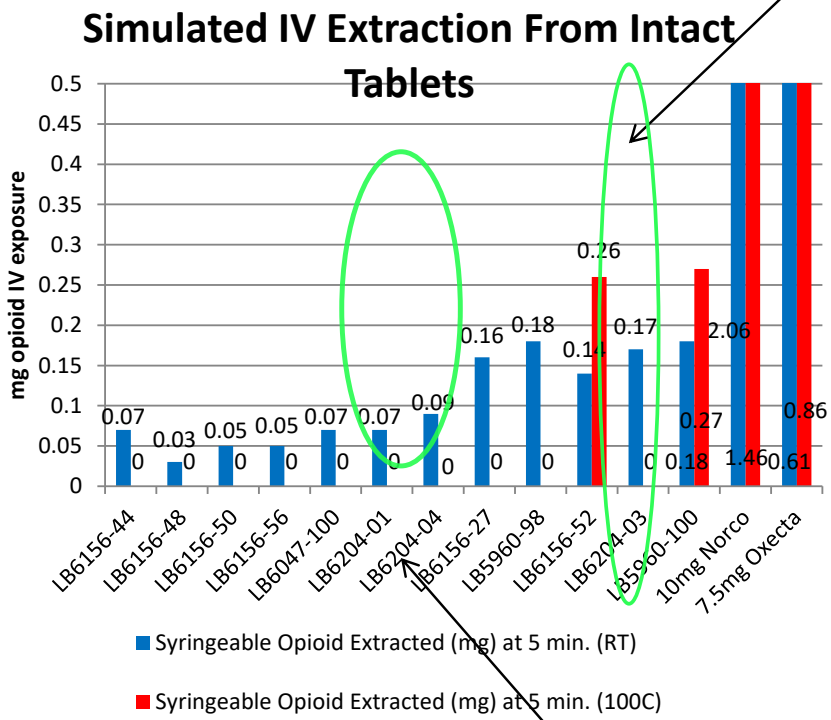
(Immediate Release tablet crushed and dissolved in nasal fluid at body Temperature)

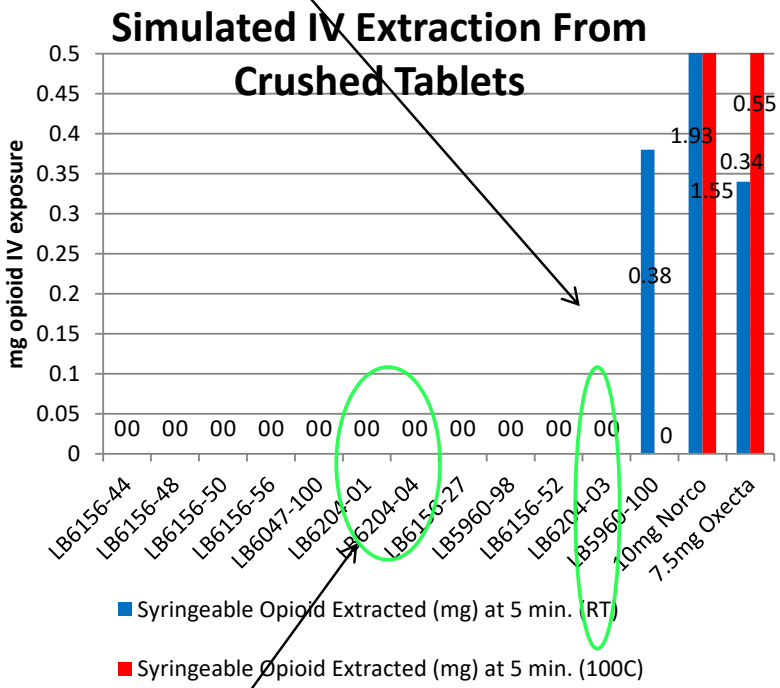


Source: Internally generated data, part of AD1 development program

IR Hydrocodone Simulated IV

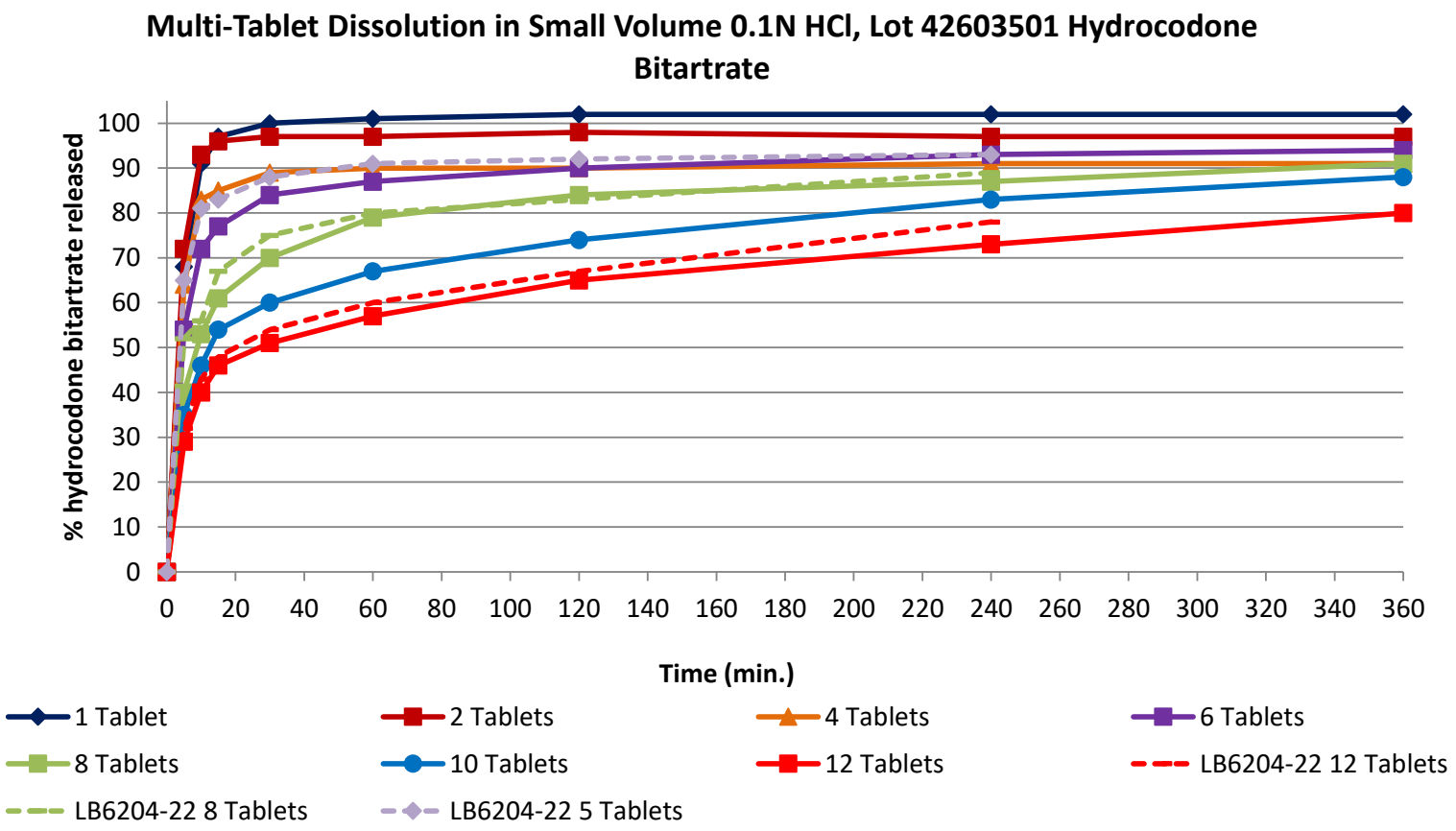
Lead Direct Compression prototype





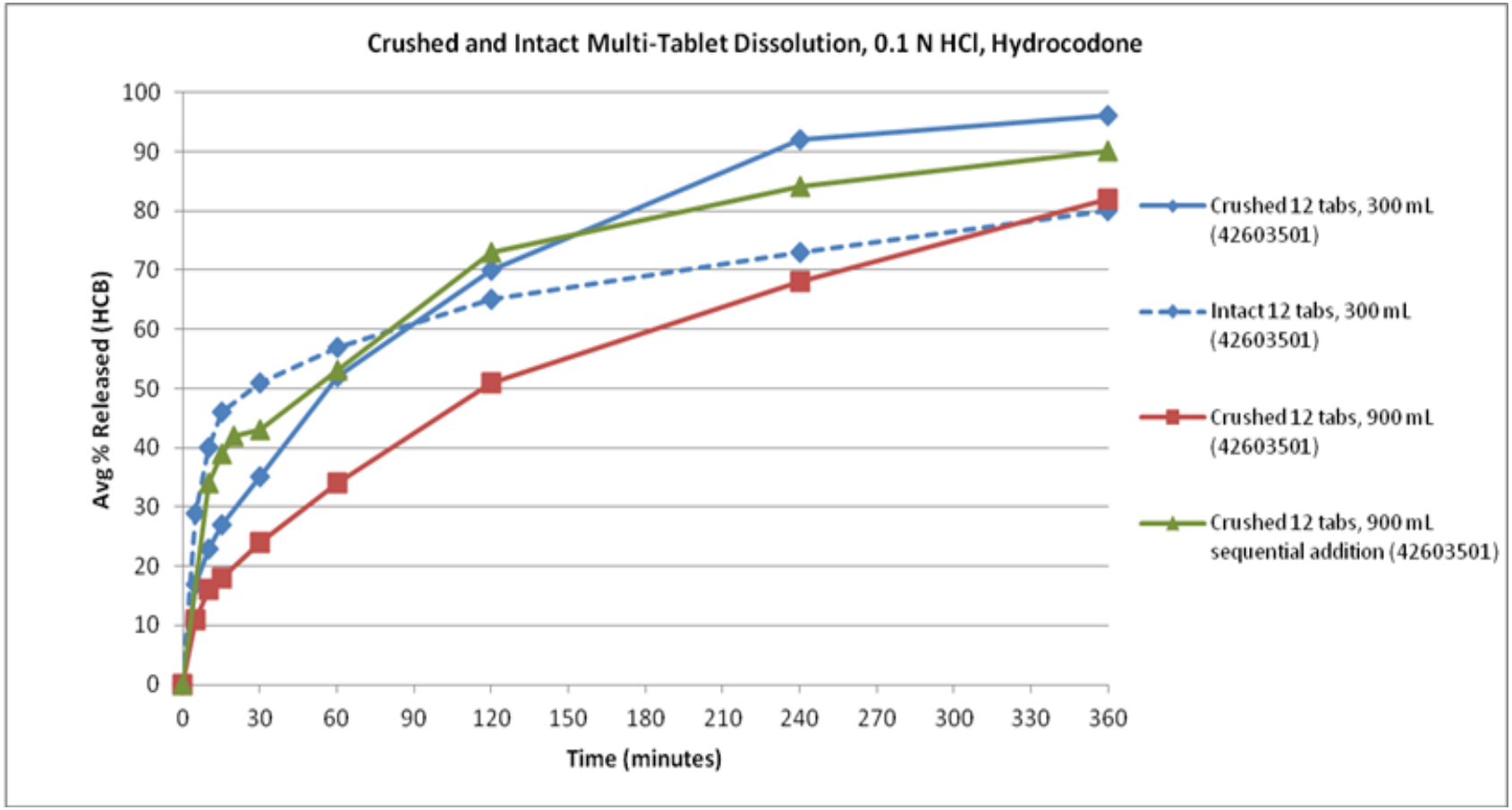
Lead Gran-Layer-Coat prototypes

10 mg Hydrocodone Multiple Tablet (MTAR) In Vitro

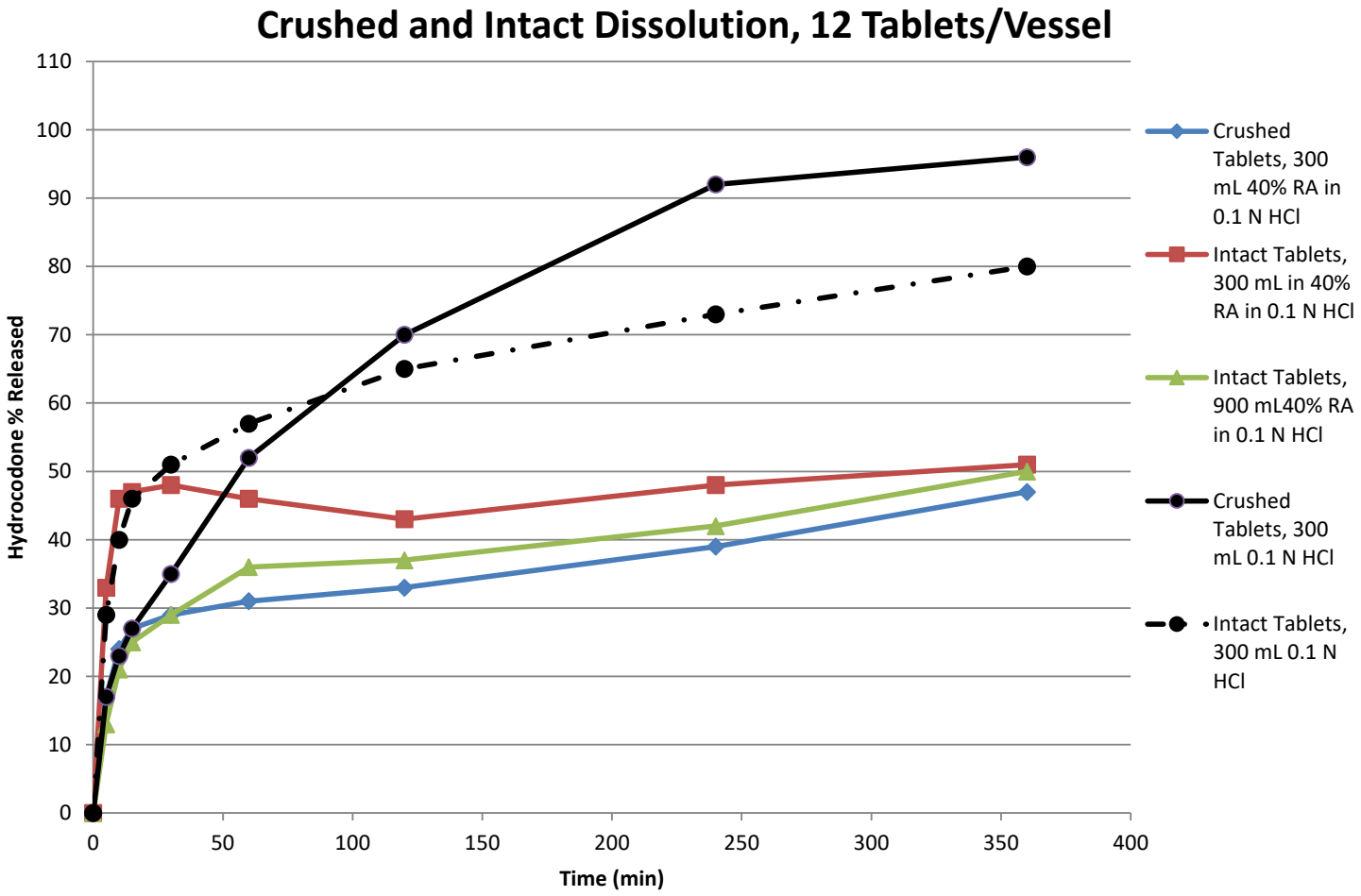


Dotted lines are the Brooklyn Park batch
Solid lines are the Salt Lake City batch

Crushed Multiple Tablet Data



MTAR: 40% Alcohol Medium (12 tablets)



Cold Water Extraction (CWE)

- Method
  - Crushed IR OraGuard HCB/APAP tablet(s) stirred in cold (5 °C) media for 10-30 minutes
  - Refrigerated
  - Filtered through a pre-wetted coffee filter under vacuum
    - Filtrate volume recorded
  - Assayed for HCB and APAP content

Cold Water Extraction (CWE)

Ratio of APAP to hydrocodone in intact 10/325 mg tablet = 32.5

# of 10/325 Tablets	Cold Water Volume (mL)	Volume Filtrate Obtained (mL)	% HCB Dose Recovered	% APAP Dose Recovered	APAP/HCB Ratio
1	40	2	1.8% (0.18 mg)	2.5% (8.1 mg)	45
1	45	6	5.1% (0.51 mg)	3.1% (10.2 mg)	20
1	100	0	NA	NA	NA
1	200	90	26% (2.6 mg)	43% (141.2 mg)	54
10 Norco	25	NR	71% (71 mg)	9% (293 mg)	4

Agenda

Section	Presenter	Time
Breakfast		8:00-8:30
Welcome and Introduction	Heather Schoenly	8:30-8:45
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Close	Jeff Dierks	12:10-12:15
Lunch		12:15-1:00

Product Overview

Maciej Gasior, M.D., Ph.D.
Clinical Project Physician

Unmet Medical Need

- Immediate Release (IR) products containing hydrocodone are indicated for the treatment of patients with moderate to moderately severe acute pain
- IR Hydrocodone is most commonly found in combination with acetaminophen
  - NORCO® (Actavis)
  - VICODIN® (AbbVie)
  - LORTAB® (UCB)

- Due to the alarming increase in the abuse, misuse, and diversion of opioid products in the US, there is a large unmet need for abuse deterrent (AD) opioid formulations which will reduce the risk of both oral and non-oral routes of abuse

The impact of opioid abuse is staggering

In the United States…

Sources: Multiple. Listed in speaker notes page

Unmet Medical Need (cont.)

- Abuse of IR Hydrocodone formulations
  - IR formulations abused most frequently by their intended oral ROA:
    - Hydrocodone: 87-100% oral, 18-40% inhalation, ≤1% injection
    - Oxycodone: 83% oral, 44% inhalation, and 0.5% injection
  - IR formulations more likely abused intact (e.g., over ingestion); ER formulation more likely to be manipulated for abuse

- The FDA recognizes opioid abuse/misuse as a serious public health problem, has been supportive of the development of these abuse deterrent formulations, provided draft guidance and begun to limit non-abuse deterrent extended release formulations. It is predicted that the abuse of IR formulations and patch formulations will increase as ER formulations become more uniformly abuse deterrent

TV-46763

- Hydrocodone bitartrate + acetaminophen
- Same dosage strengths as Norco
  - 5.0/325 mg
  - 7.5/325 mg
  - 10/325 mg
- Abuse Deterrent (AD) properties using OraGuard™ Drug Delivery Technology (coated granulation formed into a compressed tablet)
- The goal is:
  - “Norco-like” analgesic for treating moderate to severe acute pain with added AD properties

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Clinical Pharmacology

Mary Bond

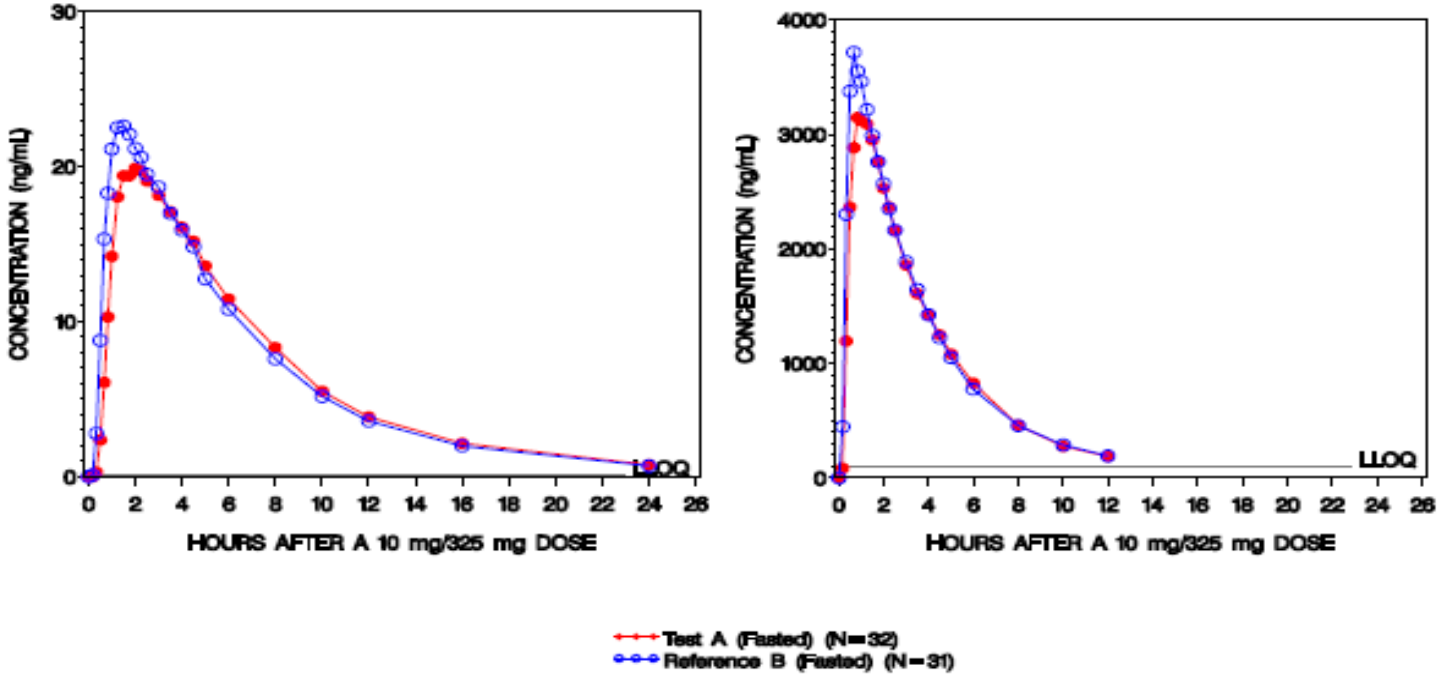
Goals of Clinical Pharmacology & Biopharm Studies

- Basic PK characterization
  - Single and multiple dose PK profile
  - Food effect
  - Dose proportionality
  - Relative bioavailability
    - Relevant commercially available combination product: Norco
    - Reference drugs for 505(b)2 submission pathway
      - ✓ Vicoprofen (hydrocodone)
      - ✓ Ultracet (acetaminophen)
- Category 2 data
  - Multiple intact tablets taken orally
  - Insufflated PK
- Category 3 data
  - Oral liking study
  - Intranasal liking study

Basic Pharmacokinetic Characterization

Single Dose PK Profiles: TV-46763 vs Norco (Fasted)

- Overall exposure to hydrocodone and acetaminophen is comparable
- Rate and extent of absorption of hydrocodone and acetaminophen differs
  - Peak concentrations of hydrocodone and acetaminophen occur slightly later (45 and 20 minutes, respectively) and are 10%-15% lower following administration of TV-46763



Source: Study 11436004.
Note: For both figures, red circles indicate hydrocodone (fasted) and blue circles indicate NORCO (fasted).

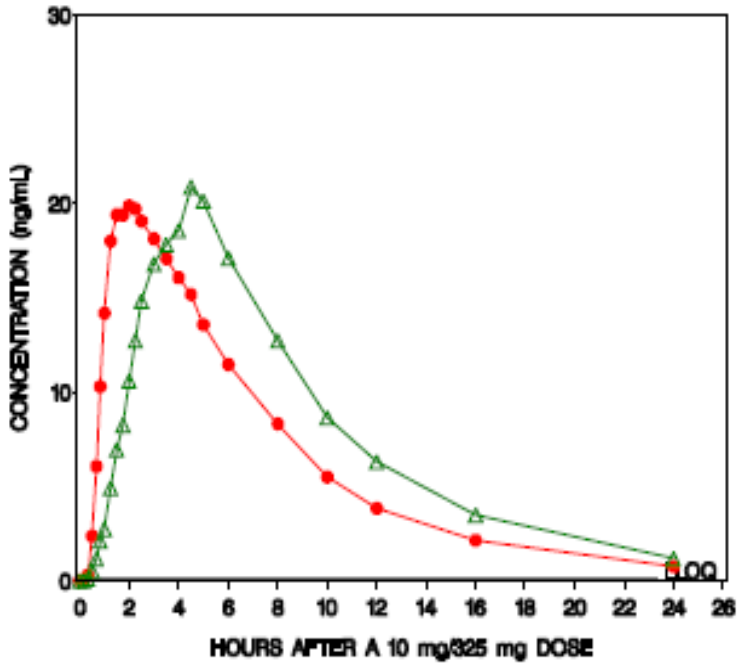
Single Dose PK Parameters: TV-46763 vs Norco (Fasted)

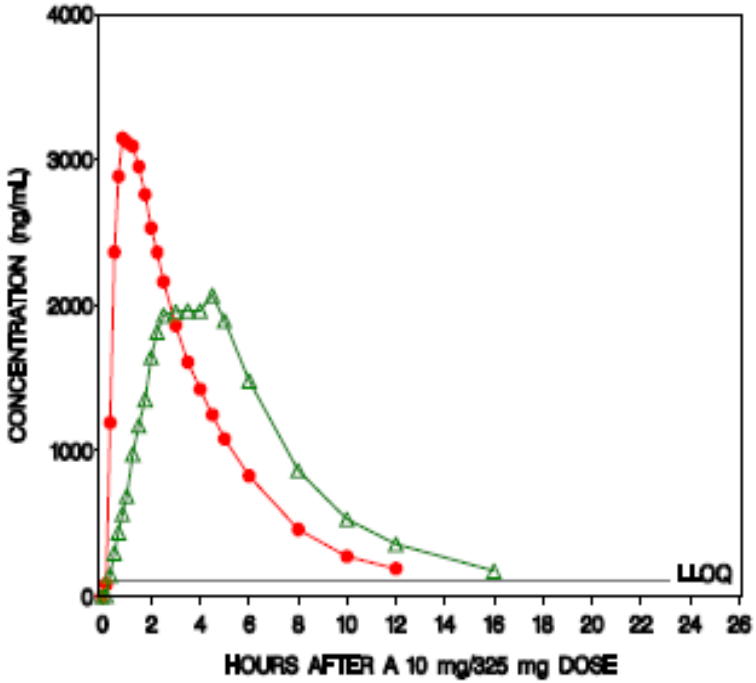
Parameter	Treatment	Hydrocodone			Acetaminophen		
		Geometric Mean	Ratio	90% CI	Geometric Mean	Ratio	90% CI
C_{max}	TV-46763	20.98	0.88	0.78, 0.99	3409	0.87	0.76, 0.99
	NORCO	23.83			3906		
AUC_{0-t}	TV-46763	141.4	0.94	0.83, 1.07	12829	0.93	0.83, 1.05
	NORCO	149.9			13769		
$AUC_{0-\infty}$	TV-46763	146.5	0.95	0.84, 1.07	13590	0.93	0.83, 1.05
	NORCO	154.6			14587		
$AUC_{0-reftmax^*}$	TV-46763	7.646	0.56	0.48, 0.64	726.2	0.61	0.50, 0.76
	NORCO	13.76			1183		
AUC_{0-1}	TV-46763	3.824	0.45	0.38, 0.54	1712	0.73	0.62, 0.85
	NORCO	8.406			2357		

Source: Study 11431044.
CI=confidence interval; ISCV=intra-subject coeffcient of variance.
reftmax=fasting acetaminophen: 0.6667 hours, fasting hydrocodone 1.2500 hours; fed acetaminophen: 1.2500 hours, fed hydrocodone: 1.6250 hours.

Single Dose PK Profiles: TV-46763 vs Norco (Fed)

- When TV-46763 is administered with a high-fat meal, peak and overall exposure to hydrocodone is comparable to that observed in a fasted state; however, median t_{max} is delayed to 4 hours
- When administered with food, the pharmacokinetics of acetaminophen are also affected. C_{max} is approximately 29% lower and occurs later (median of 2.5 hours)





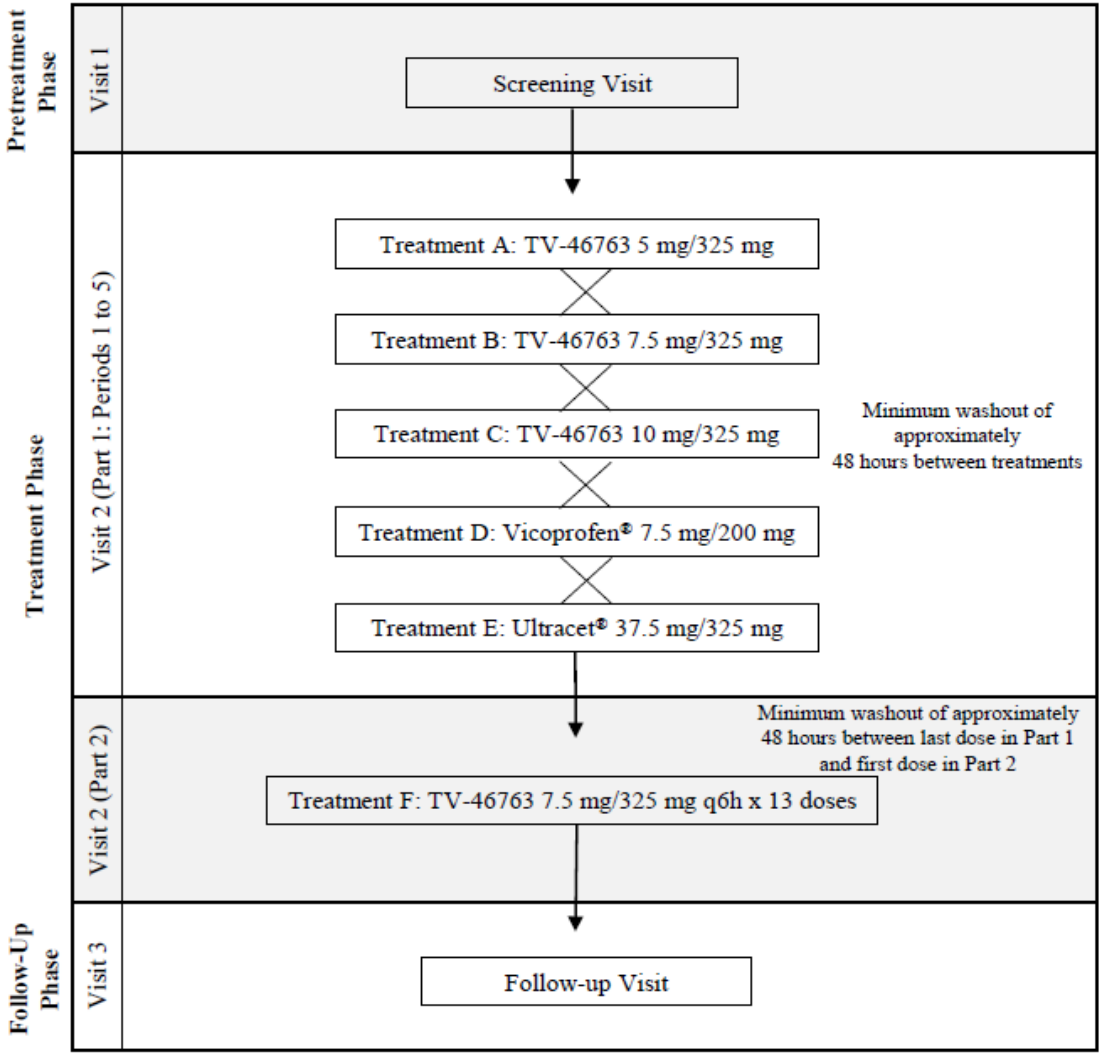
Source: Study 11436004.
Note: For both figures, red circles indicate fasted and green triangles indicate fed.

Single Dose PK Parameters: TV-46763 vs Norco (Fed)

Parameter	Treatment	Hydrocodone			Acetaminophen		
		Geometric Mean	Ratio (fed vs. fast)	90% CI	Geometric Mean	Ratio (fed vs. fast)	90% CI
C_{max}	TV-46763 fast	21.90	1.04	0.99, 1.09	3570	0.71	0.66, 0.77
	TV-46763 fed	22.75			2542		
AUC_{0-t}	TV-46763 fast	150.9	1.15	1.09, 1.21	13939	1.01	0.97, 1.06
	TV-46763 fed	173.3			14070		
$AUC_{0-\infty}$	TV-46763 fast	156.4	1.165	1.09, 1.23	14969	1.02	0.97, 1.06
	TV-46763 fed	181.0			14929		
$AUC_{0-reftmax^*}$	TV-46763 fast	7.322	0.294	0.16, 0.53	708.8	0.47	0.30, 0.74
	TV-46763 fed	2.149			332.5		
AUC_{0-1}	TV-46763 fast	3.581	0.10	0.05, 0.19	1695	0.10	0.06, 0.17
	TV-46763 fed	0.3713			174.9		

Source: Study 11431044.

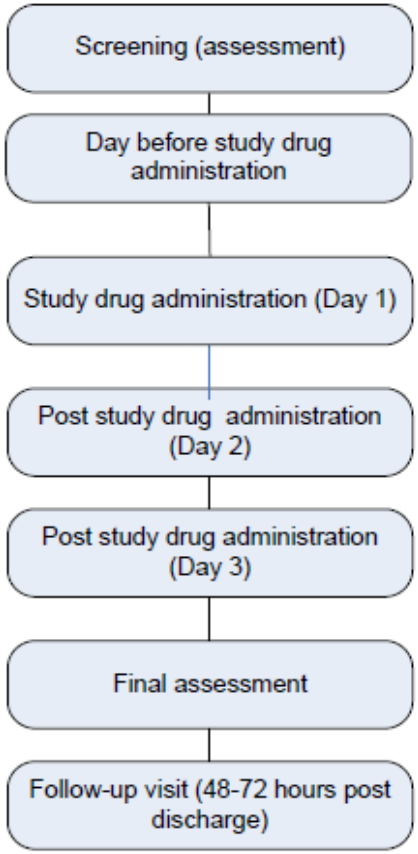
Multiple Dose PK, Dose Proportionality, Relative BA



Category 2 Data

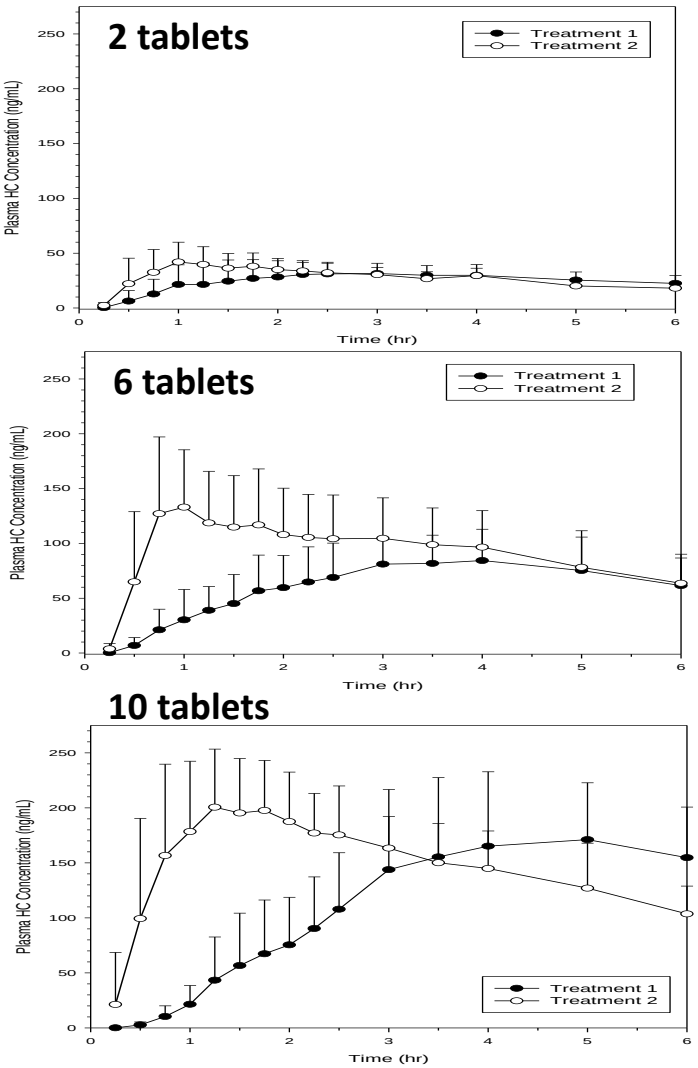
Multiple Tablet PK study - Design

An Open-label, Randomized, Single Ascending Dose Study to Compare the Pharmacokinetics and Safety of Simultaneous Oral Administration of Multiple Tablets of TV-46763 or NORCO® in Healthy Naltrexone-Blocked Subjects.



Clinical Multiple Tablet PK Data

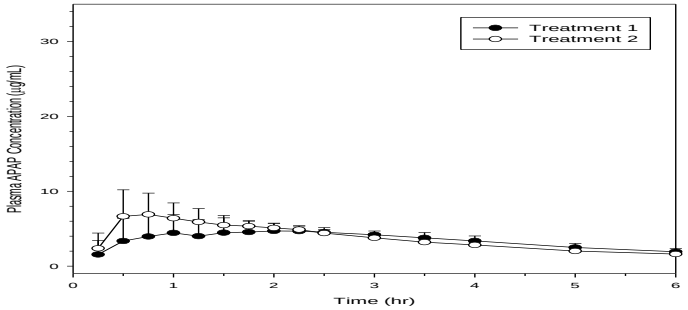
- Study designed to determine if in vitro data translates in vivo
- Escalated through 10 tablets with no safety signals identified
- Results demonstrate:
  - Two tablet cohorts are comparable NORCO
  - Noteworthy differentiation in hydrocodone exposures as compared to NORCO (commercially available reference product) over the first 2-4 hours at ≥ 6 tablets



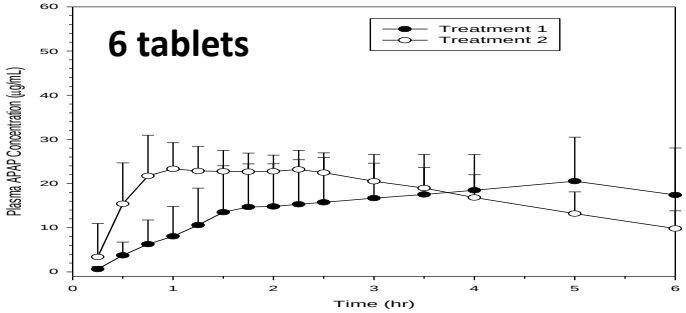
Clinical Multiple Tablet PK Data (cont'd)

- Similar differences in profiles for acetaminophen
- Lower earlier exposure to both hydrocodone and APAP may mitigate risks in an overdose situation and allow more time for medical intervention

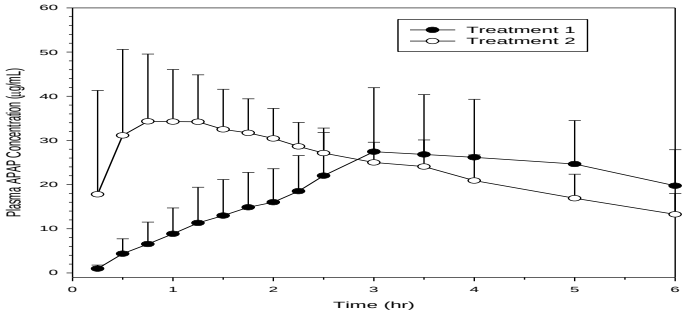
2 tablets



6 tablets

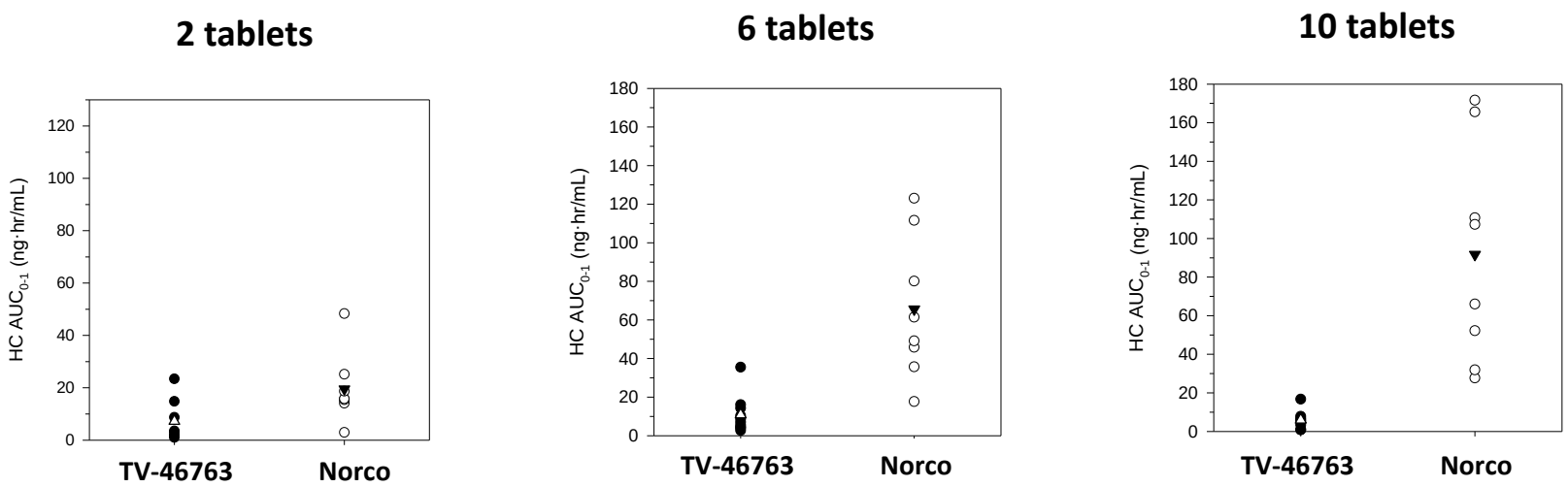


10 tablets



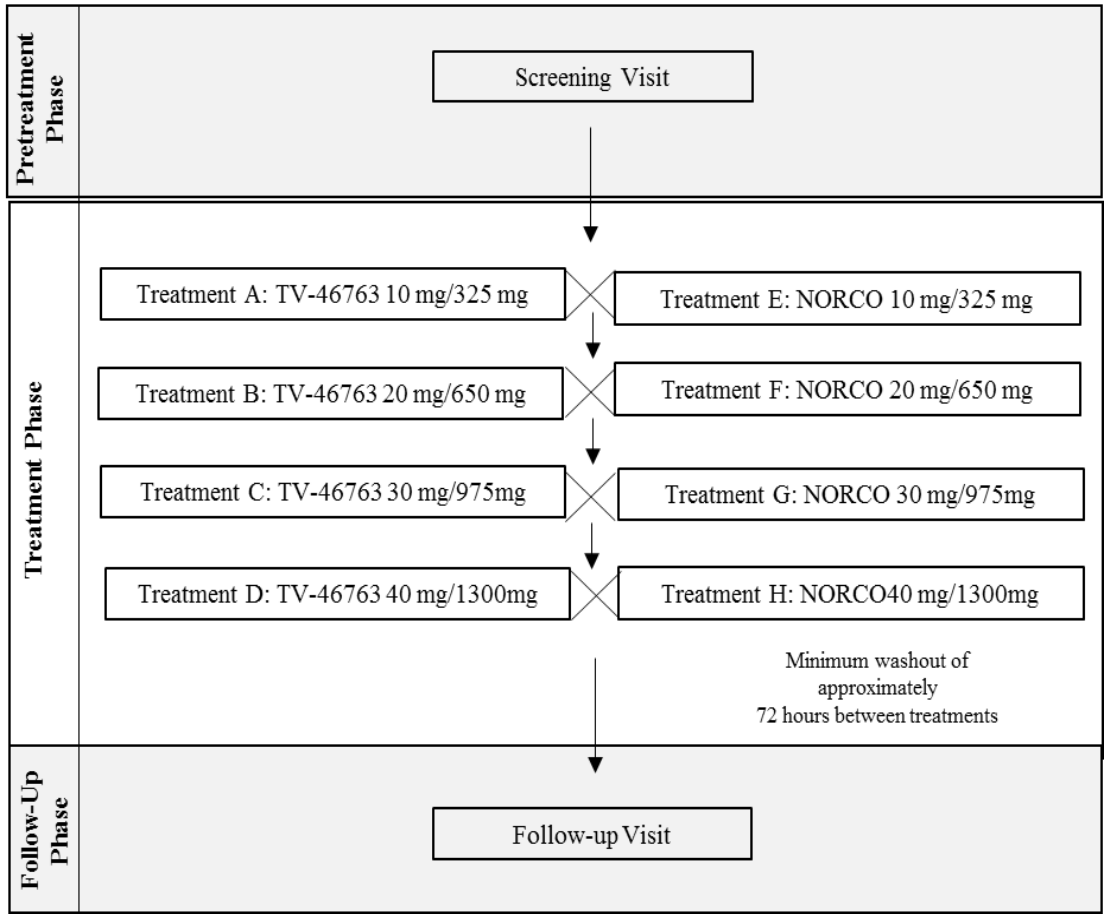
Clinical Multiple Tablet PK Data (cont'd)

- To claim abuse deterrence, statistically less liking to a relevant comparator must be demonstrated in a human abuse liability (HAL) study
- Early exposure to opioid (rate & extent of rise) is most relevant in terms of drug liking
- TV-46763 is well differentiated from NORCO at ≥ 6 tablets (a dose used in previous HALs)



Intranasal PK study - Design

An Open-label, Randomized, Single Ascending Dose Study to Compare the Pharmacokinetics and Safety of Simultaneous Oral Administration of Multiple Tablets of TV-46763 or NORCO® in Healthy Naltrexone-Blocked Subjects.



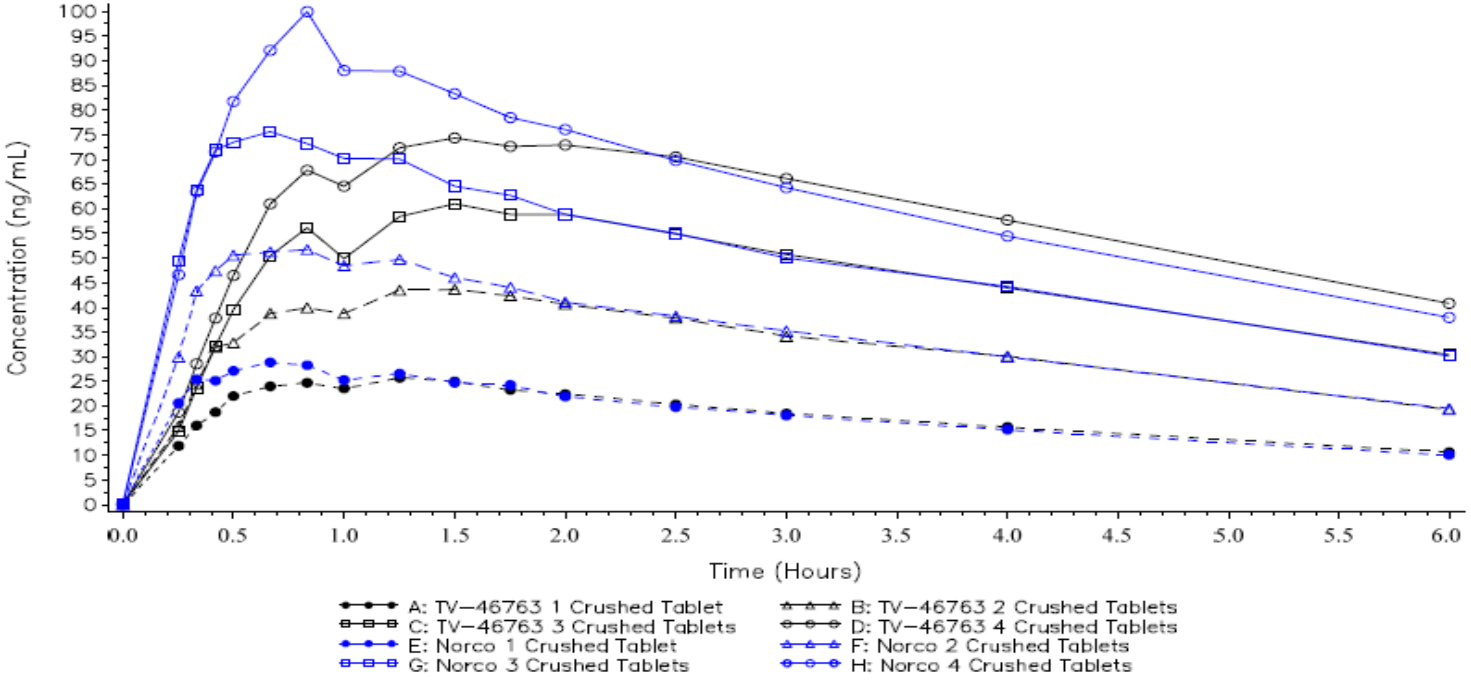
Comparison of Amount Insufflated: TV-46763 vs NORCO

- Nearly all subjects were able to insufflate 4 tablets of NORCO
- Nearly half or more than half of the subjects were unable to insufflate 3 or 4 tablets of TV-46763

Number of Tablets	Number of Subjects Unable to Insufflate/Total Number of Subjects	
	TV-46763	NORCO
1 Tablet	1/30	0/30
2 Tablets	5/30	0/30
3 Tablets	12/28	1/29
4 Tablets	15/28	1/28

Insufflated PK profiles: TV-46763 and NORCO

- Hydrocodone exposure increased < proportionally for both products; however, the lack of proportionality was more pronounced for TV-46763 than for NORCO
- Within each dose level, overall exposure was not grossly different but peak concentrations were lower and occurred later for TV-46763
- Early exposure was lower for TV-46763, particularly in the first hour
- Differences between TV-46763 and NORCO most apparent at 3 and 4 tablets



Note: Figure only includes data for subjects able to insufflate the entire dose.

Insufflated PD data: TV-46763 and NORCO

- Drug Liking
  - TV-46763: showed little increase above neutral ("At the Moment") or was notably lower than Neutral (Overall) across the full range of doses
  - NORCO: values at all dose levels were indicative of drug liking with the extent increasing with increase in dose for Norco
- Trends confirmed by the results of the "take drug again" assessment

Assessment and Statistic		TV-46763 (1 Tablet) (A)	TV-46763 (2 Tablets) (B)	TV-46763 (3 Tablets) (C)	TV-46763 (4 Tablets) (D)	NORCO (1 Tablet) (E)	NORCO (2 Tablets) (F)	NORCO (3 Tablets) (G)	NORCO (4 Tablets) (H)
Peak Drug Liking (At the Moment)	Mean (SD)	63.8 (14.53)	56.7 (22.21)	62.3 (15.37)	60.1 (22.82	72.0 (17.10)	77.7 (16.59)	82.6 (19.26)	86.4 (14.47)
	Median (Range)	60.5 (49.0, 94.0)	59.0 (3.0, 100.0)	59.0 (22.0, 99.0)	63.5 (3.0, 100.0)	70.0 (44.0, 100.0)	76.5 (50.0, 100.0)	84.0 (10.0, 100.0)	89.0 (51.0, 100.0)
Overall Drug Liking	Mean (SD)	35.2 (24.11)	35.3 (27.58)	31.9 (26.22)	28.9 (26.19)	68.2 (20.32)	72.9 (23.22)	72.8 (28.99)	77.7 (19.79)
	Median (Range)	47.5 (0.0, 73.0)	35.5 (0.0, 99.0)	31.0 (0.0, 81.0)	25.0 (0.0, 77.0)	66.0 (33.0, 100.0)	76.5 (2.0, 100.0)	79.5 (0.0, 100.0)	81.0 (42.0, 100.0)
Take Drug Again	Mean (SD)	34.4 (27.01)	32.8 (28.76)	29.5 (26.69)	28.1 (24.55)	65.2 (24.64)	73.4 (24.43)	75.1 (27.37)	79.9 (21.52)
	Median (Range)	44.5 (0.0, 94.0)	28.0 (0.0, 86.0)	25.0 (0.0, 86.0)	20.5 (0.0, 81.0)	62.5 (4.0, 100.0)	77.5 (0.0, 100.0)	83.5 (0.0, 100.0)	88.5 (22.0, 100.0)

Assessments presented on bipolar 100-point visual analog scale (VAS) (0=maximum negative response, 50=neutral response, 100=maximum positive response).

Insufflated PD data: TV-46763 and NORCO

- Overall, NORCO was easier and more pleasant to snort as compared to TV-46763
- Subjects more likely to use NORCO again as compared to TV-46763
- As the number of tablets per dose increased, subjects viewed NORCO in a more favorable light. In contrast, TV-46763 was viewed less favorably as the number of tablets per dose increased

Parameter (at 0.25 hours post-dose)	TV-46763 (1 Tablet) (A)	TV-46763 (2 Tablets) (B)	TV-46763 (3 Tablets) (C)	TV-46763 (4 Tablets) (D)	NORCO (1 Tablet) (E)	NORCO (2 Tablets) (F)	NORCO (3 Tablets) (G)	NORCO (4 Tablets) (H)
Ease of Snorting	73.5 (0.0, 100.0)	83.0 (3.0, 100.0)	89.5 (8.0, 100.0)	99.0 (66.0, 100.0)	26.0 (0.0, 77.0)	12.0 (0.0, 75.0)	15.0 (0.0, 98.0)	9.5 (0.0, 51.0)
Pleasantness of Snorting	68.0 (0.0, 100.0)	82.5 (34.0, 100.0)	90.0 (14.0, 100.0)	98.0 (65.0, 100.0)	45.0 (0.0, 91.0)	26.5 (0.0, 100.0)	24.0 (0.0, 94.0)	12.5 (0.0, 54.0)
Likelihood of Further Use	40.0 (0.0, 100.0)	11.0 (0.0, 100.0)	10.5 (0.0, 90.0)	2.5 (0.0, 76.0)	57.0 (2.0, 100.0)	74.5 (1.0, 100.0)	90.0 (4.0, 100.0)	94.5 (39.0, 100.0)

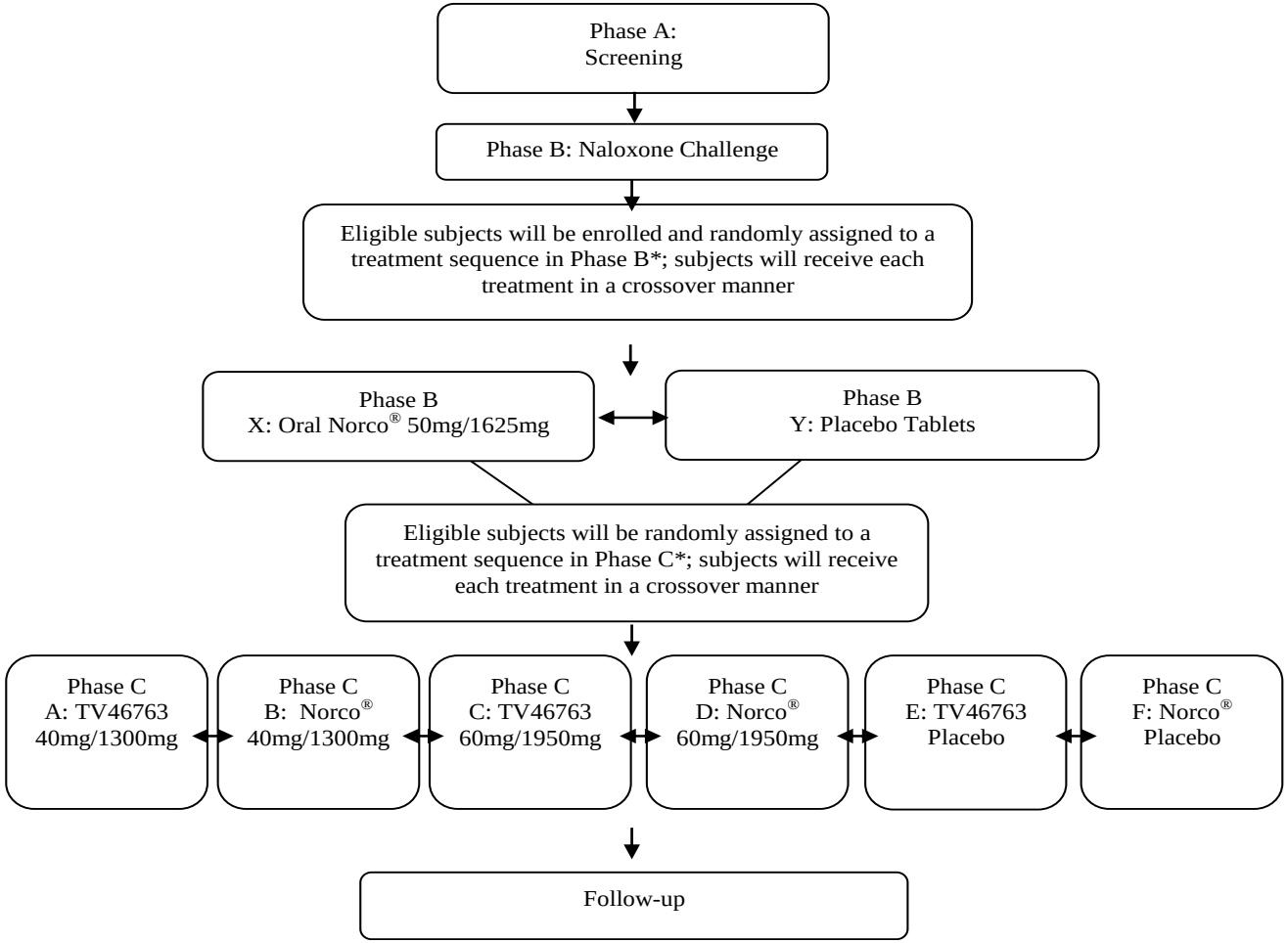
Abbreviations: NORCO = reference product; VAS = Visual Analog Scale.
Note: Bipolar VAS: 0= Very Easy, 100=Very Difficult; 0=Very Pleasant, 100=Very Unpleasant; 0=Definitely Would Not, 100=Definitely Would
Note: Values presented are median (range).

- TV-46763 produced more severe and sustained nasal effects (intranasal irritation, burning, need to blow nose, runny nose/nasal discharge, facial pain/pressure, and nasal congestion)

Category 3 Data

Oral Liking Study Design

A Randomized, Double-Blind, Placebo and Active-Controlled, Single-Dose, Crossover Study to Assess the Abuse Potential, Safety, and Pharmacokinetics of TV46763 Following Oral Administration of Multiple Intact Tablets to Healthy, Nondependent, Recreational Opioid Users



Objectives/Comparisons

- PD Objectives/Comparisons:
  - Primary:
    - TV-46763 vs NORCO at each dose level based on Emax of "At the Moment" liking
  - Secondary:
    - TV-46763 vs NORCO at each dose level based on all secondary measures
    - Low dose vs high dose TV-46763 based on primary and secondary measures
    - Low dose vs high dose NORCO based on primary and secondary measures
  - Placebo control: establishes study validity, frequency and magnitude of changes in absence of active, and minimizes subject and investigator bias

- Other Secondary Objectives:
  - PK of all treatments
  - Safety of all treatments

E_{max} for "At the Moment Liking" (numerous time points)

These comments relate to the drug effects you are experiencing right now. Mark a clear perpendicular line across each horizontal line depending on how you feel at this moment.

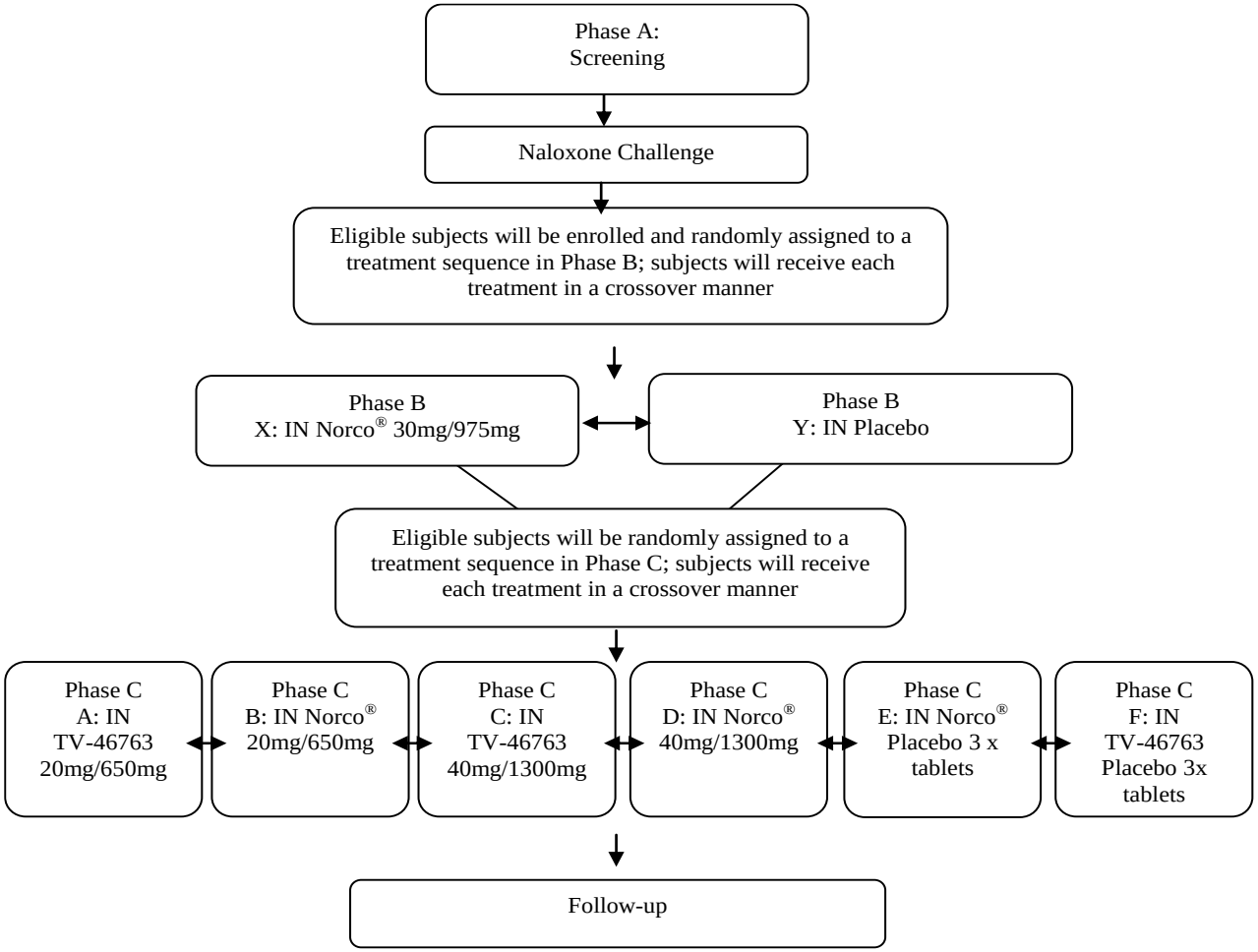
1. **My liking for this drug is:**

Strong Disliking |_____|_____| **Strong Liking**

Neither like nor dislike

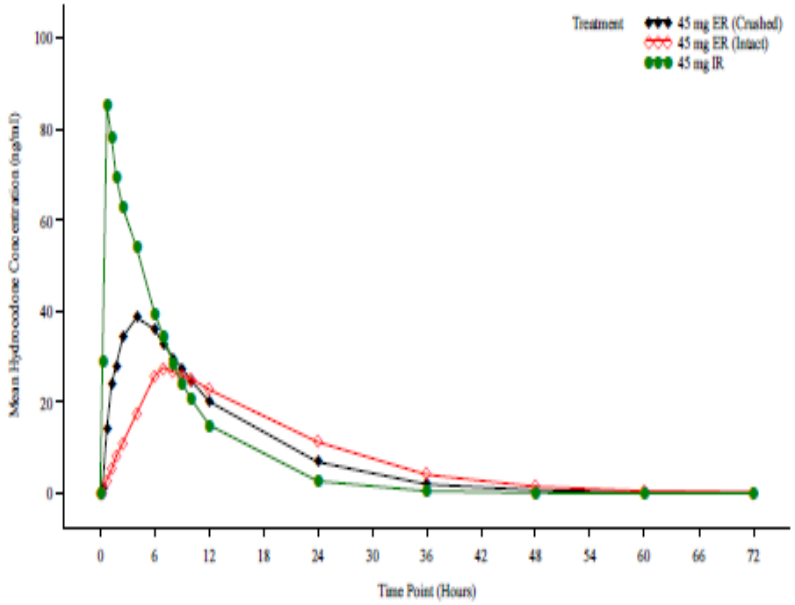
Intranasal Liking Study Design

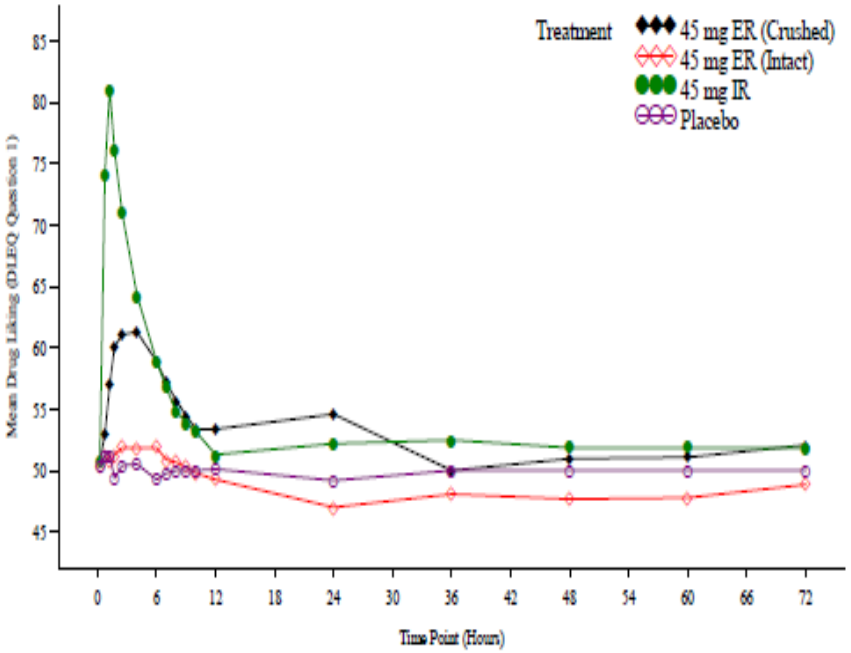
A Randomized, Double-Blind, Placebo and Active-Controlled, Single-Dose Crossover Study to Assess the Abuse Potential, Safety, and Pharmacokinetics of TV-46763 Following Intranasal Administration by Healthy, Nondependent, Recreational Opioid Users



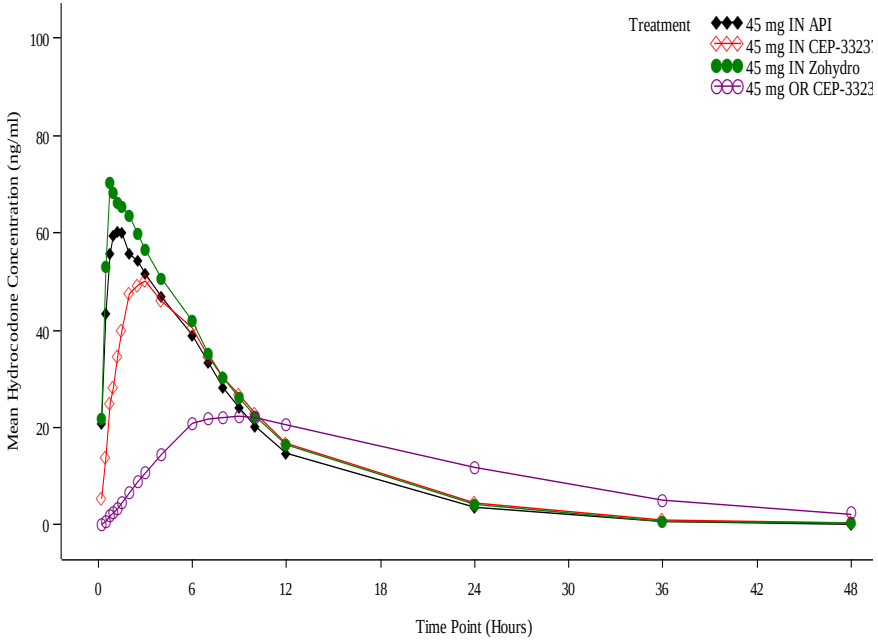
Example Category 3 Study Results from ER Hydrocodone

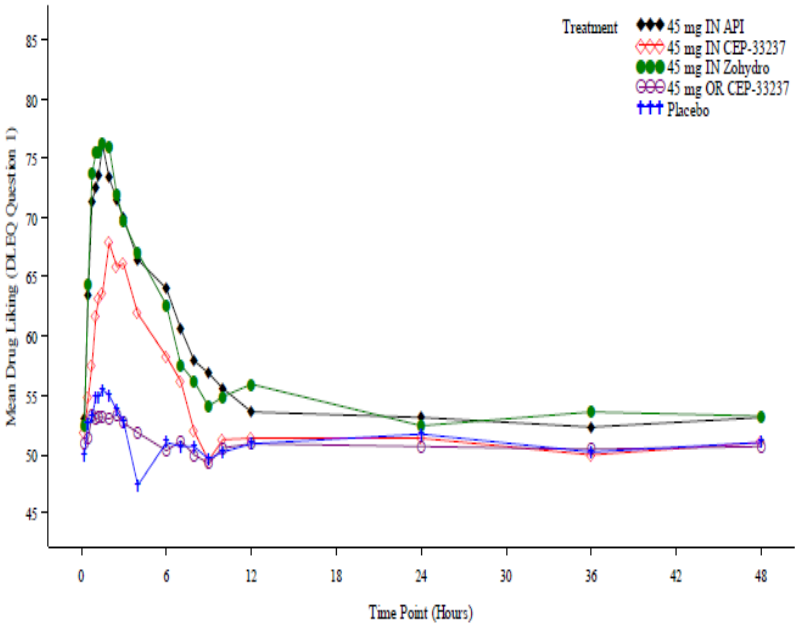
Example Oral Liking Study Results - PK & PD (ER Hydrocodone)





Example Intranasal Liking Study Results - PK & PD (ER Hydrocodone)





Phase III Studies

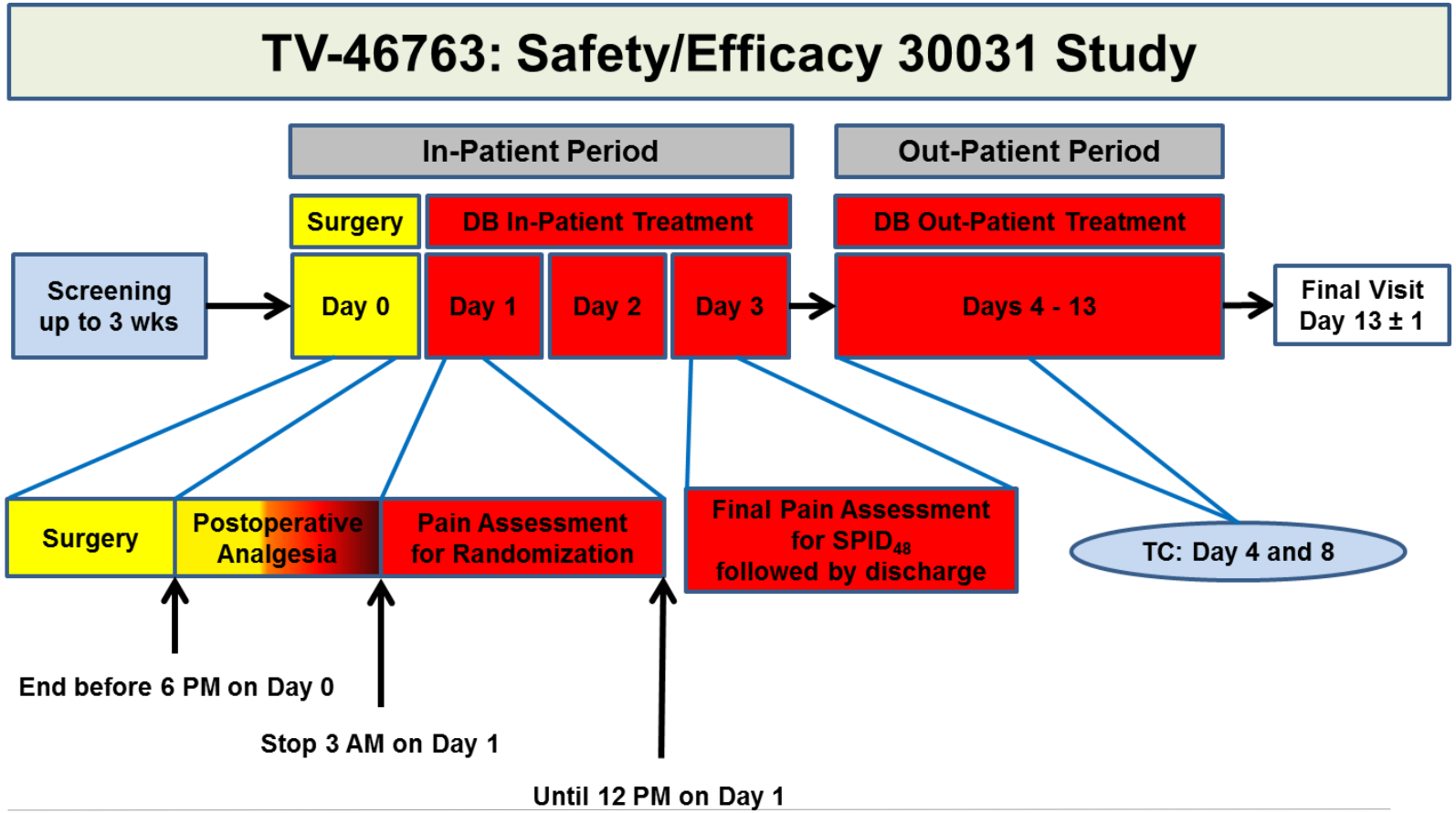
Maciej Gasior, M.D., Ph.D.
Clinical Project Physician

Agenda

- Summary of study design
- Study population
- Number of patients planned
- Study endpoints

Summary of study design

A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Evaluate the Analgesic Efficacy and Safety of Hydrocodone Bitartrate/Acetaminophen Immediate-Release Tablets (TV-46763) at Doses of 5.0 mg/325 mg, 7.5 mg/325 mg, and 10 mg/325 mg Every 4 to 6 Hours in Patients with Moderate to Severe Pain Following Bunionectomy



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Study population

Men and women aged 18 to 75 years, inclusive, who are scheduled to undergo a primary unilateral first metatarsal Austin bunionectomy with distal osteotomy and internal fixation without any collateral procedures (ie, uncomplicated procedure) may be eligible for inclusion in the study if, in the opinion of the investigator, they are in generally good health with no uncontrolled chronic illness or disease (as determined by a medical history, medical examination, electrocardiogram [ECG], serum chemistry, hematology, urinalysis, and serology) and if they meet all screening, pre-operative, and postoperative inclusion criteria for the study and none of the exclusion criteria.

Number of patients planned

- It is planned to **screen approximately 836** patients to have approximately **560 patients randomized** (140 patients in each of the 4 treatment groups)
- Eligible patients will be randomly assigned via interactive response technology (IRT) in a 1:1:1:1 ratio to receive 1 of the following 4 treatments:
  - **Treatment A**: 5.0 mg/325 mg of hydrocodone bitartrate/acetaminophen IR tablets
  - **Treatment B**: 7.5 mg/325 mg of hydrocodone bitartrate/acetaminophen IR tablets
  - **Treatment C**: 10 mg/325 mg of hydrocodone bitartrate/acetaminophen IR tablets
  - **Treatment D**: **matching placebo tablets**
- All tablets, regardless of strength, will be white and will have the same capsule shape, weight, and size. Tablets will be debossed with “T 123” on one side and “1/234” on the other side

Primary efficacy endpoint

Summed pain intensity difference (SPID) scores calculated over the first 48 hours ($SPID_{48}$) on an 11-point numerical pain rating scale (NPRS-11), where 0=no pain and 10=the most intense pain imaginable

Secondary efficacy endpoints

- **To evaluate the analgesic efficacy of TV-46763** tablets administered every 4 to 6 hours for 48 hours compared with placebo in patients with moderate to severe pain following bunionectomy as assessed by:
  - time-interval weighted **SPID** scores calculated over **0-6, 0-12, 0-24, and 0-36** hours after the first dose of study drug
  - **PID at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 12, 24, 36, and 48 hours** after the first dose of study drug
  - **time to peak PID** after the first dose of study drug but before the second dose of study drug
  - number and proportion of **patients with a 30% and 50% reduction in pain intensity** (NPRS-11) scores at 2, 4, 6, 12, 24, and 48 hours after the first dose of study drug
  - **time to perceptible (ie, onset of pain relief) and meaningful** pain relief after the first dose of study drug, using the 2-stopwatch technique
  - **time to first use of rescue medication** (oral nonprescription ibuprofen)
  - **total rescue medication** (oral nonprescription ibuprofen) **use over 6, 12, 24, and 48 hours** after the first dose of study drug
  - **number and proportion of patients taking rescue medication** (oral nonprescription ibuprofen) **over 6, 12, 24, and 48 hours** after the first dose of study drug

Exploratory/Other Endpoints

- To assess **WPI24 daily** starting on day 2 through day 13±1 day or early termination, based on NPRS-11

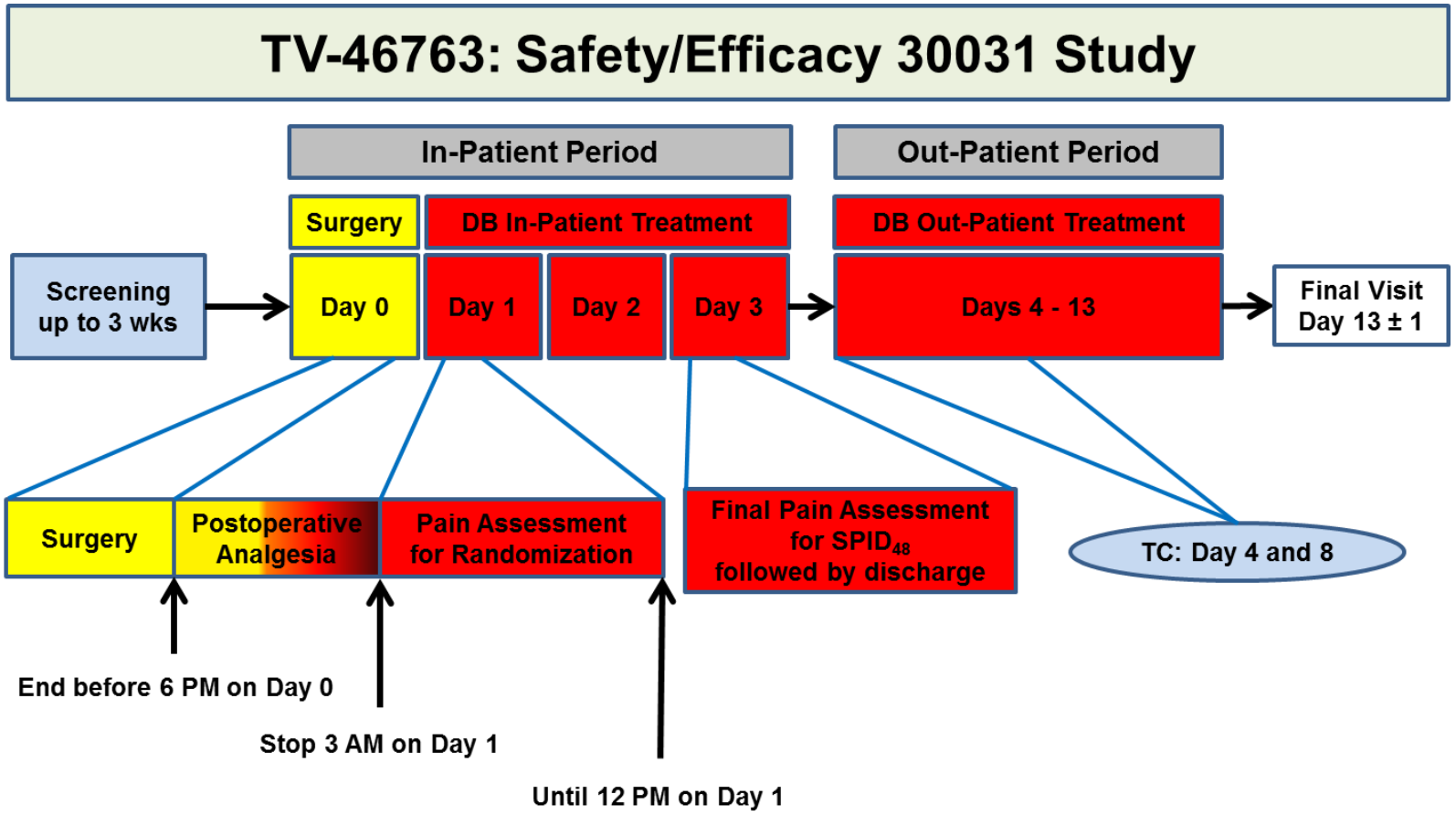
- **Global Assessment of Patient Satisfaction** at day 3 (discharge) and day 13±1 day or early termination to assess the patient's satisfaction with treatment across 5 dimensions (ie, ease of administration, dosing frequency, number of tablets taken, time for medication to work, level of pain relief) on a categorical scale (ie, very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, or very dissatisfied)

- The incidence of drug loss and diversion during the outpatient treatment period

Safety endpoints

- **Occurrence of adverse events**, beginning when the patient signs the informed consent form/opioid agreement, until day 13±1 day or early termination
- **Physical examination findings** on days 0, 3 (discharge), and 13±1 day or early termination
- **Vital signs** (blood pressure, pulse, respiratory rate, and SpO2) on days 0, 1, 2, 3 (discharge), and 13±1 day or early termination
- 12-lead **ECG** on days 0, 3 (discharge), and 13±1 day or early termination
- **Clinical laboratory evaluations** (serum chemistry, hematology, and urinalysis) on days 0, 3 (discharge), and 13±1 day or early termination
- **Concomitant medication** usage throughout the study
- **Suicidality** based on investigator's assessment of patient's responses to the C-SSRS scores on days 0, 3 (discharge), and 13±1 day or early termination

General design



Regulatory Affairs

Jennifer Pansch

TV-46763 US Regulatory Milestones

- Achieved
  - Original IND submitted Oct over 2013, open in November 2013
  - End of Phase 2 Type B FDA meeting, conducted 22 Apr 2015

TV-46763 End of Phase 2 Meeting Outcomes

- FDA had concerns with the food effect (delayed Tmax) and was insistent that there would be a food restriction on the label
- FDA suggested our existing PK data, though not BE, were “close enough” for a BE approach to be viable, and seemed to encourage this approach at the meeting
- However, the formal written minutes present the acceptability of a BE approach more as a possibility than a probable scenario
  - FDA declined to define criteria for “close enough” and that it would be best to meet standard BE criteria
  - FDA stated that if we conduct the additional recommended BE study, they would review the results, and then recommend whether an efficacy study would be required
  - Given recent FDA study review times, pursuing this approach could negatively impact timeline

TV-46763 End of Phase 2 Meeting Outcomes

- FDA offered surprising little guidance or objections on the AD aspects of the program
- Their recommendation for the oral HAL study was easy to implement (add a second, lower dose)
- FDA is re-evaluating relevance of nasal abuse for APAP-containing IR opioids
  - FDA would not state whether or not a nasal HAL study is necessary for registration, or whether such a study would merit label claim
- Teva left with a clear understanding of CMC and Nonclinical registration requirements
- TV-46763 is exempt from PREA (pediatric) study requirements
- Overall, the meeting was collaborative and productive

TV-46763 Next Steps

- Application for Fast Track Designation July 2015
  - Based on potential abuse deterrence, with special focus on oral intact abuse resistance
  - May allow improved communication with the division, the possibility for rolling NDA submission, and possibility of priority review
- Pre-NDA Type B Meeting 2Q2016
- NDA submission August 2016
  - Eligible for Priority Review (6 month review) if no AD HC/APAP IR products have been approved at the time of our submission
  - Otherwise, standard review timelines would be expected (10 months)

TV-46763 Registration Plan

- 505(b)(2) NDA
- Teva will reference the FDA's previous findings of safety and efficacy of 2 NDA products
  - Reference NDA Drug for Hydrocodone: Vicoprofen
  - Reference NDA Drug for Acetaminophen: Ultracet
- This is a unusual regulatory situation, as there are no IR HC/APAP products that were approved under an NDA; all currently approved HC/APAP products are ANDA products and cannot be used as references for this purpose
  - However, FDA agreed that Norco can be employed as reference for therapeutic combination of hydrocodone and APAP
  - Norco will also be used for a comparator in AD studies

TV-46763 Registration Plan

- Teva will need to provide all the elements of a standard NDA (CMC, nonclinical, clinical pharmacology, and safety/efficacy information) to assure that it is a safe, effective, and well-controlled high quality product
  - All standard regulatory requirements apply!
- AD labeling will require extensive abuse potential assessment (in vitro, PK, HAL) for relevant routes of abuse
- Teva will seek AD label claims based on in vitro data (IV, extractions, separations) and based on our human studies (intact oral abuse and nasal PK and HALs)
- FDA will review totality of data in NDA to determine whether AD claims are appropriate
- Other AD products approved before our product may shift the regulatory expectations for AD studies for our product

Regulatory Exclusivity

- TV-46763 may be eligible for 3 years of data exclusivity if:
  - FDA considers our Ph 3 “necessary for approval”
    - Not a certainty, given mixed messages about the BE approach
  - FDA awards exclusivity for our AD studies
    - Far from a certainty (precedence to date: n = 1)
- Blocking (b)(2) exclusivity concerns that could affect approval of our NDA
  - No currently approved products would appear to block ours
  - If other HC/APAP products are approved before ours, and they are granted regulatory exclusivity, there could be issues depending on their conditions for approval
  - Converting our application to a (b)(1) application to circumvent blocking (b)(2) exclusivity would be more challenging. Right reference would be required for both actives, or full (b)(1) studies

TV-46763 Regulatory Challenges with AD products

- FDA's "Abuse Deterrent Opioids– Evaluation and Labeling" guidance is primarily focused on ER products intended to deter manipulation of the dosage form
  - Useful guidance for nasal and IV studies
  - Not helpful for most IR products
  - Not helpful for intact oral studies
- FDA's current understanding of AD products is largely shaped by data on other products (primarily ER) that they have reviewed
- FDA's expectations are shifting:
  - FDA guidance published 2 April indicated that nasal abuse was not relevant for APAP-containing opioids
  - By 22 April, FDA would no longer opine whether nasal abuse is or isn't relevant
- AD strategy will need to be continuously re-evaluated and the development adapted as needed

Post-marketing AD Regulatory Commitments

- If TV-46763 is allowed pre-marketing AD label claims, we will be required to conduct post-marketing epidemiologic studies to monitor abuse and further assess the abuse potential of the drug in the community to verify the AD formulation works as expected
  - Can the AD features be easily circumvented and therefore are not providing any deterrence?
  - Monitor for unintended consequences (e.g., increased IV abuse of Opana after reformulation)
  - These studies will be quite extensive
  - There is opportunity for Teva to obtain the strongest AD label claim with sufficient epidemiologic data ("These data demonstrated a reduction in the abuse of TV-46763 in the community setting…")
  - No one yet has achieved this strongest AD claim; there is an upcoming AdCom to discuss Purdue's epi data

Example Label Claims

- Indication: " TV-46763 is indicated for the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate."
- AD claims:
  - "The in vitro data demonstrate that TV-46763 has physical and chemical properties that are expected to deter intravenous abuse and extraction. The data from the clinical abuse potential studies, along with support from the in vitro data, also indicate that TV-46763 has physicochemical properties that are expected to reduce intranasal abuse and oral abuse when multiple tablets are swallowed. However, abuse of TV-46763 by the intravenous, intranasal, and oral routes is still possible." (Section 9)
  - Descriptions of AD in vitro and clinical study data (Section 9)
- Actual TV-46763 claims will be based on our study results and FDA agreement

So What About Overdose!?

- Overdose technically means taking more than prescribed; TV-46763 does not prevent that
- A mu-agonist cannot prevent or protect against poisoning from opioid overdose. It is not an antagonist (e.g., Narcan). At best, there would be less overdose risk
- However, FDA will not allow a “safer” or “less risk from overdose” label claim based on premarketing data
  - Controlled clinical studies to compare the safety of patients when overdosed could not be ethically be conducted
  - PK cannot be used to prove greater opioid safety; it must be correlated to PD effect
- Comparing differences in overdose-related AEs when therapeutically prescribed to patients will require very large studies not typically feasible premarketing
  - This will need to be built into our post-marketing studies

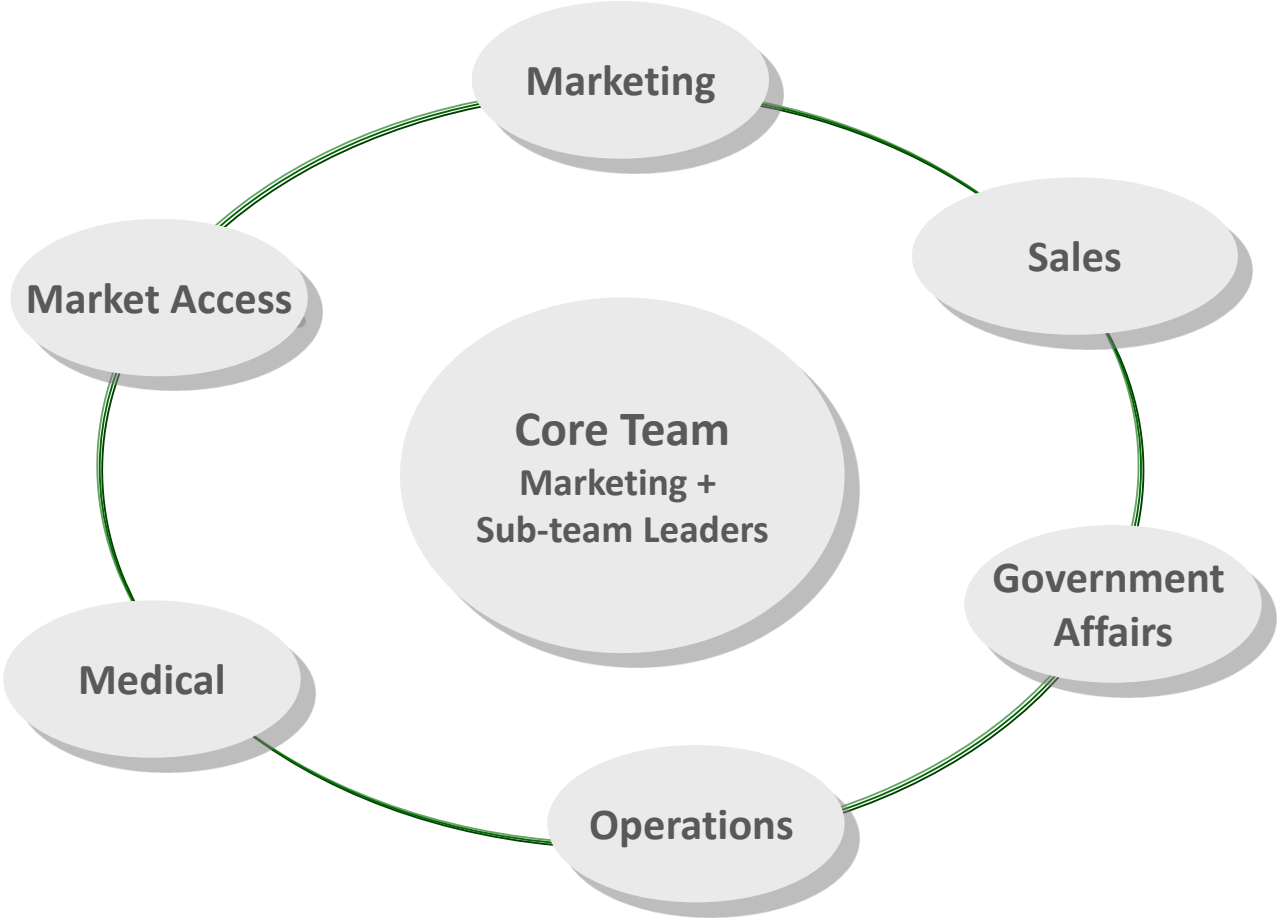
So What About Overdose!?

- Opportunities based on premarketing data might include:
  - Multiple Tablet Oral AD claims (section 9, previously addressed)
  - PK profiles after ingestion of supratherapeutic dose, compared to conventional tablet (section 12.3)
  - Respiratory parameters after supratherapeutic dose, compared to conventional tablet (section 12.2)
  - Differences in overdose management, compared to conventional tablet (section 10)
  - Language in Dosage and Administration (section 2) describing that drug release is delayed if more than the label dose is prescribed
  - Patient information describing that taking more than the prescribed dose will slow onset of the medication
- Stronger label claims may be possible based on strong post-marketing epidemiologic data

Launch Governance

Heather Schoenly

Current Team Structure



IR Hydro and IR Oxy – single work stream at initiation

IR Hydrocodone Launch Governance

Steering Committee

- John Hassler (General Manager)
- Jeff Dierks (Marketing)

Core Team

- Alex Nikas (Legal)
- Deb Bearer (Market Access)
- Derek Moe (Operations)
- Dorit Mimrod (R & D)
- Doug Harnish (Regulatory)
- Heather Schoenly (Brand Lead)
- Jeff Dierks (Marketing)
- Jim Reilly (Sales)
- Matt Day (Brand Lead)
- Matt Wieman (Medical)
- Yousseff Khan (Market Research)

Sub-Teams

Marketing/ Market Research	Heather Schoenly (Co-Lead), Yousseff Khan (Co-Lead), Agencies, Doris Saltkill, Jeff Dierks, Karen Hill, Matt Day, Shannen Kelly
Medical	Matt Wieman (Lead), Chirag Shah, Jessica McLin, Kavita Gajria, Matt Day
Market Access	Deb Bearer (Lead), Chris Doerr, Erica Fischer, George Keefe, Heather Schoenly, Jay Simpson, Katie Hiett, Kavita Gajria, Nick Penzetta, Rob Falb, Yousseff Khan
Sales/Sales Training/ Sales Operations	Jim Reilly (Lead), Chris Meyer, Jay Rojohn, Joe Smith, Marc Oseroff, Matt Day, Peter Wilson, Robert Krutsick
Operations	Lois Rongstad (Lead), Bob Nield, Chris Doerr, Colin Edwards, Corey Wall, Derek Moe, Heather Schoenly, Joe Smith, Joel Childs, Meirav Marom, Sharon Jones, Tal Lehrmann
Government Affairs	Rob Falb , Erica Fisher, Heather Schoenly, Jerry Moore Karen Hill, Matt Day, Rob Kincaid *(Lead TBD)*

Extended Team (Summit)

- (Agencies)
- Amy Ross (Compliance)
- Anupam Singh (Digital)
- Chirag Shah (Medical Affairs)
- Chris Doerr (Trade)
- Chris Meyer (Sales Ops)
- Dana Kelley (Finance)
- Doris Saltkill (Communications)
- Elizabeth Seltzer (Pharmacovigilance)
- George Keefe (Market Access)
- Jessica McLin (Medical Affairs)
- Jim Ciciriello (Regulatory)
- Jim King (Medical Information)
- Joe Smith (Forecasting)
- Karen Hill (Advocacy)
- Kavita Gajria (HEOR)
- Lois Rongstad (Operations)
- Marc Oseroff (Sales Training)
- Martin Stanell (IT)
- Nate Capone (Medical Affairs)
- Nick Penzetta (Market Access)
- Pete Wilson (Sales Ops)
- Rob Falb (Government Affairs)
- Shannen Kelly (Marketing- IR Oxy)

* Launch Management is a member of all teams

Team Roles and Responsibilities

Steering Committee

- Process oversight
- Issue resolution
- Approval of high-level decisions

Core Team

- Review and prioritize sub-team recommendations
- Drive and lead strategic planning, implementation, refinement and tracking
- Ensure alignment and coordination of activities

Sub-Team

- Develop and implement strategic and tactical recommendations
- Ensure alignment with brand strategy and positioning
- Make recommendations to core team on launch plan

Hydrocodone ER (Vantrela ER) Launch Dashboard

Date	June 9, 2015
Promotional Launch Date	TBD (Dec 2015 or Feb 2016)

On track

Nov 2014: Begin intermediate validation

Feb 21: FDA acceptance of application

May 13: APS conference

Sep: PAINWEEK

Oct 23: PDUFA

Oct-Nov: Bottling of batches (QA release)

Nov 2014 — **Jan 2015** — **Dec 2015**

Dec 23: FDA submission

Mar 11: Day 74 letter from FDA with PDUFA date

Mar 18: Pain Matters Campaign Launched

May 23: FDA mid-cycle review

Nov: OPDP submission

TBD: Commercial Launch (Dec or Feb)

Recent Accomplishments

- Pending Agreement in place with Abbvie for right of reference to Vicoprofen NDA (Regulatory/Legal)
- American Pain Society Meeting attended (convention booth/breakfast & afternoon symposia) (Marketing)
- 2nd round of VANTRELA ER message testing completed (Marketing)
- Final Report of 2nd round Concept testing provided (Marketing)
- 7 PainWeekend programs completed to date (Marketing)
- Team presented 5 abstracts at American Pain Society meeting (Medical)
- Phase IV Trial reviewed by Medical Affairs review committee
- Team kicked off exploratory research to guide formulary and cost messaging for HCPs and Reimbursement Coordinators (Market Access)
- Presented initial Pricing recommendations to leadership (Market Access)
- 2016 AOP Project kicked off for CNS BU (single product/marketing mix assessment) (Sales)
- Sales Training Module 1 Approved with changes (Sales)
- Abuse Deterrence (AD) Prescription Coverage bill submitted in 33 states for approval (approved in 7 states UT, CO, TN, IN, MA, VA, MD)
- 30 mg product validation batches produced and shipped to VA; 15, 60 & 90 mg batches packaged in VA (Operations)

Upcoming Activities

- Team waiting on FDA questions/comments related to Mid-Cycle review meeting (Regulatory)
- Pain Matters Earned Media launch scheduled for June 24
- Final VANTRELA ER Message testing report due June 3 (Marketing)
- VANTRELA ER Patient Work Plan presentation in June (Marketing)
- Team to submit 3103 manuscript to *Journal of Opioid Management* (Medical)
- HEOR Geisinger opioid and alcohol use study initial results due in June (Medical)
- Submit dose ranging HEOR study abstract to Pain Week (Medical)
- Conduct "Pain Matters" screening in Harrisburg, PA on June 9, 2015 (Government Affairs)
- Payer Insight Refresh final report due in June (Market Access)
- Value Message testing to occur in June (Market Access)
- PARC review and approval of Sales Training Modules 2-4 (Sales)
- 2016 AOP CNS BU analysis final report due in July (Sales)
- Package 30 mg validation batches in VA (Operations)
- Complete 45 mg product validation batches and ship to VA (Operations)
- Finalize tableting of NORAMCO API for each strength and begin stability testing (Operations)

G = On track Y = At-risk R = Delayed

Current Issues

- Launch status has been reset to "on track" with regards to the revised PDUFA date of Oct 23 2015
- Y FDA mid-cycle review targeted for May 23rd - as of June 4th, still awaiting comments on any deficiencies in NDA application and ability to convert from a 505b2 to a 505b1 filing. We do not perceive any atypical risks to the application and LOA remains at 90%
  - 505b1 filing route with AbbVie data package is still pending; hope to have terms finalized in June
- Possibility of December vs February launch date being explored based on PDUFA date of October 23rd. We anticipate making a decision on the launch date in the next 30 days, post the mid-cycle review feedback with the FDA.
  - In either scenario product will be in the channel and available in 2015 to meet guidance to the street communicated through IR earnings calls

Next Steps

- Initial core team meeting – Week of July 13th
- Sub-team leads 1:1s – initiating in July
- Commercial brand name identification – early September

Close

Jeff Dierks

AD IR Hydrocodone Executive Summary

US opioid market is undergoing change

- 100MM Americans affected by chronic pain (*2011 Institute of Medicine report*)
- US Opioid market ~256M prescriptions, $8B in sales (*IMS Data MAT April 2015*
  - Hydrocodone represents 117K or 43% of TRx's
- Significant societal pressure on abuse, misuse and diversion
- Hydrocodone IR reclassified from CIII to CII (October 2014)
- FDA, policy makers, state authorities endorsing AD products
- 2 additional products expected prior to launch
  - Mallinckrodt – AD ER Low Dose hydrocodone with APAP – Pending
  - KemPharm – AD IR hydrocodone with APAP – Q3 2015

Teva uniquely positioned in marketplace

Redefine the responsible Opioid product profile and become the foundation for the Teva Pain Care franchise

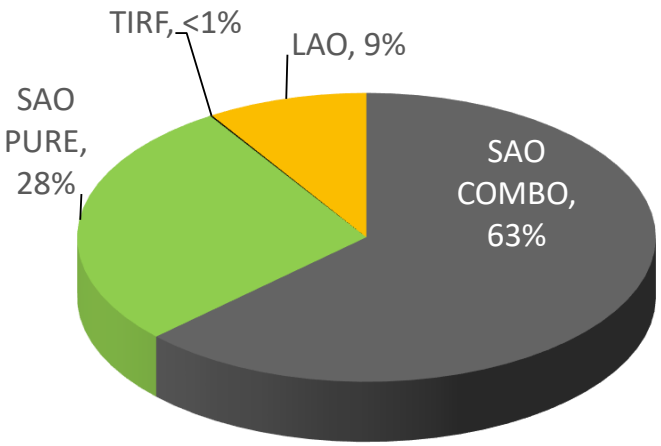
- Broaden leadership of Teva in Pain Care – beyond 'pill in a bottle'
- 1st AD IR Hydrocodone utilizing Teva proprietary Abuse Deterrent technology - MTAR
- Additional NTEs expected to in 2017-18 to further broaden portfolio

AD IR hydrocodone key strategic imperatives

- ***Educate*** stakeholders on appropriate use, abuse & AD technology
- Establish and ***differentiate*** Teva AD brand from other technology
- Develop a differentiated brand to establish ***relevance***, change/modify current behaviors and beliefs
- Ensure reimbursement access for HCPs and appropriate patients through clinical profile, value proposition and responsible/balanced education and communication re: risks and benefits
- Optimize resources through differential deployment, gated metrics

Situation Analysis: Opioid Marketplace

SAO/LAO Market:
Sales: $8.6B
Volume: 256 MM TRx
Graph Depicts Volume Share



Hydrocodone = 117MM TRx

~900K HCPs Rx IR Hydro
~46K D 3-10 HCPs Rx LAO and IR Hydro
Current PCSF Covers 11% of 46K

Market Dynamics

- 100M Americans affected by chronic pain (IOM 2011 Report)
- Opioids make up ~1/3 of U.S. chronic pain market sales
- Opioid abuse & misuse epidemic putting pressure on society, presents opportunity
  - Rescheduling of IR hydro from CIII to CII – Oct 2014
- SAO market primarily consists of generic products
- Teva uniquely positioned with IR portfolio w/AD technology

Key Competitors

Existing SAOs

- IR Hydrocodone
- IR Oxycodone
- Oxaydo

Potential Entrants

- IR hydrocodone/APAP
  - KemPharm Q3 2015
  - Elite Q4 2015
- IR oxycodone/APAP
  - Signature Thera. Preclinical

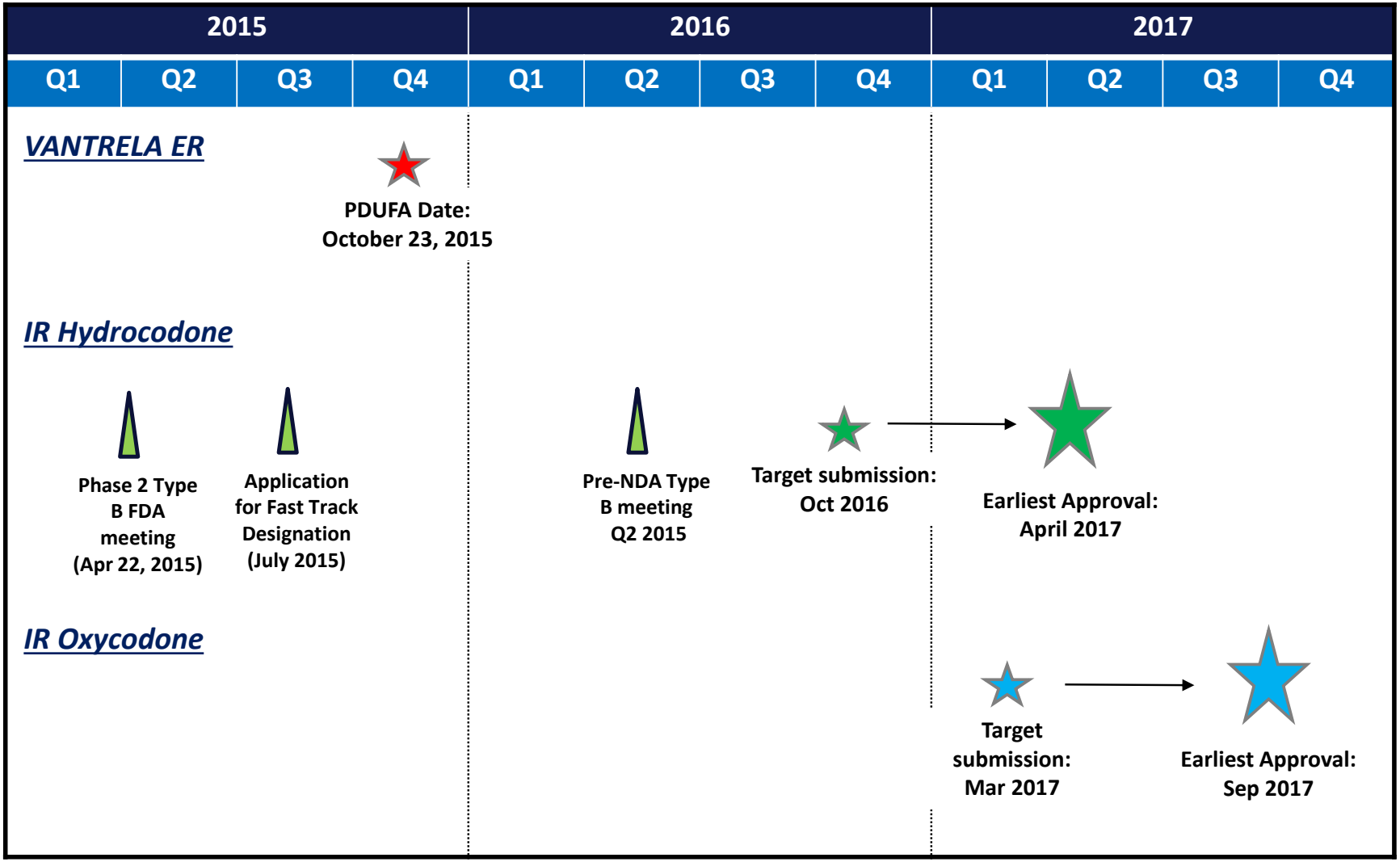
Access Landscape

- IR hydrocodone is highly genericized
- Payers do not actively manage opioids
- HEOR data needed for AD SAOs

Sources: IMS National Sales Perspectives and IMS National Prescription Audit (MAT April 2015); Institute of Medicine (2011); Decision Resources Chronic Pain Report (2013)

~403 days to the NDA Filing

Pain Regulatory Timelines



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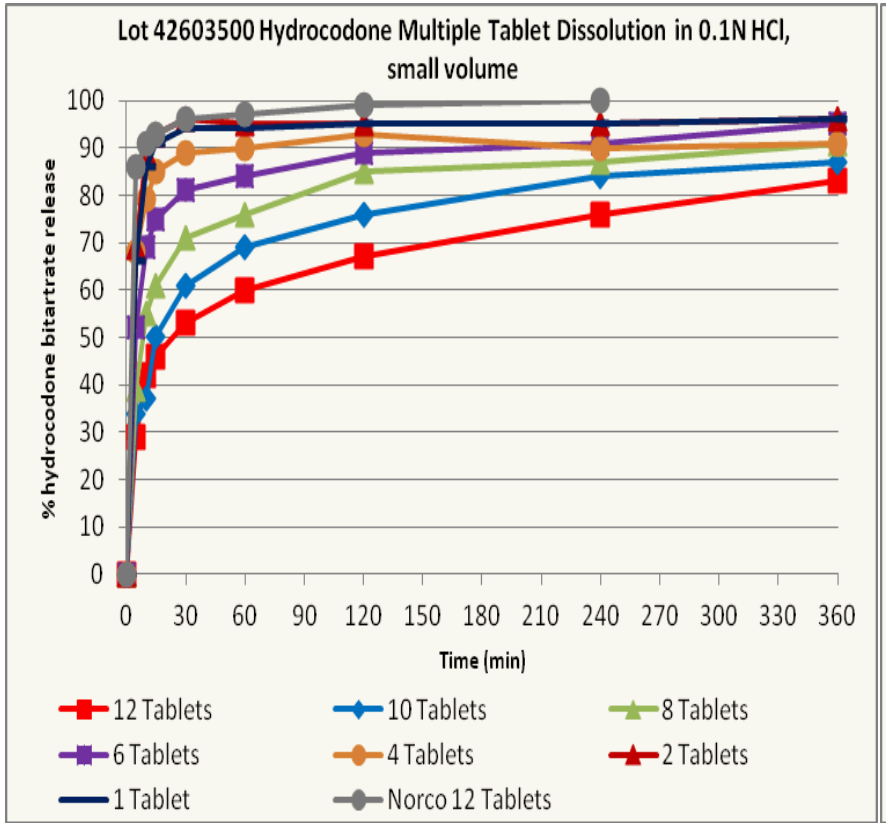
Agenda

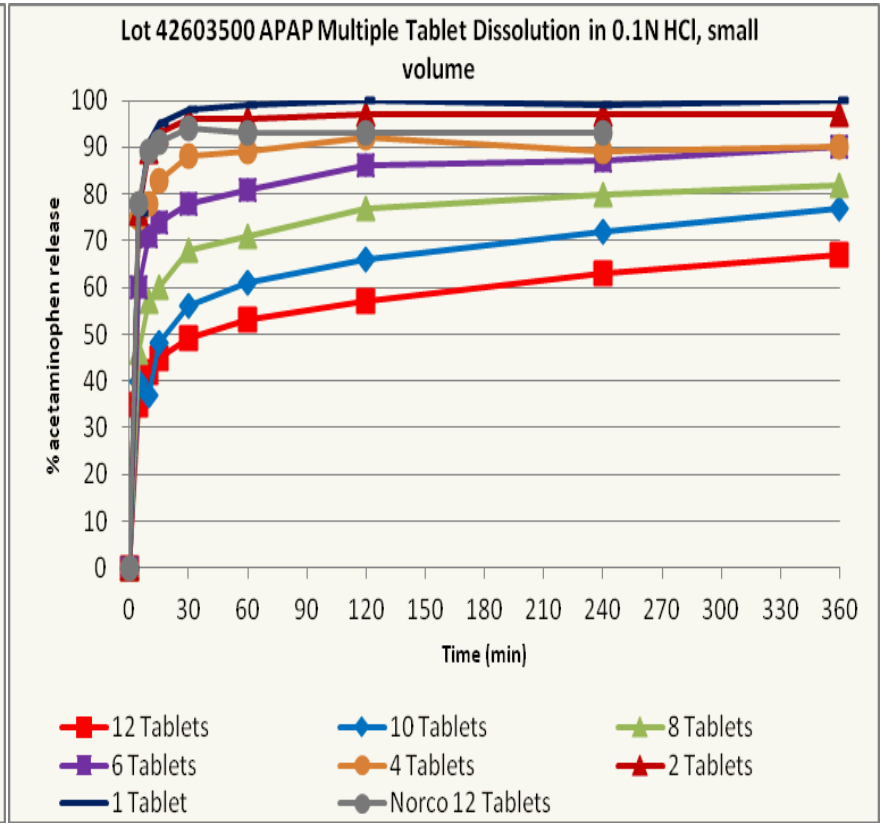
Section	Presenter	Time
Breakfast		8:00-8:30
Welcome and Introduction	Heather Schoenly	8:30-8:45
Project Overview	Dorit Mimrod	8:45-9:00
CIMA Technology/CMC	Derek Moe	9:00-9:30
Product Overview	Maciej Gasior	9:30-9:45
Break		9:45-10:00
Clinical Pharmacology	Mary Bond	10:00-11:00
Phase III Studies	Maciej Gasior	11:00-11:30
Regulatory Affairs	Jennifer Pansch	11:30-12:00
Launch Governance	Heather Schoenly	12:00-12:10
Close	Jeff Dierks	12:10-12:15
Lunch		12:15-1:00

Backup

Background: In Vitro Multiple Tablet Data

- Extended release profile is observed in vitro at ≥ 5 tablets
- Differentiates from Norco
- Differences most pronounced over first 2 hours





Hydrocodone PK Parameters (study 10028)

Mean (SD*) Pharmacokinetic Hydrocodone Parameters following Administration of TV-46763 and Norco

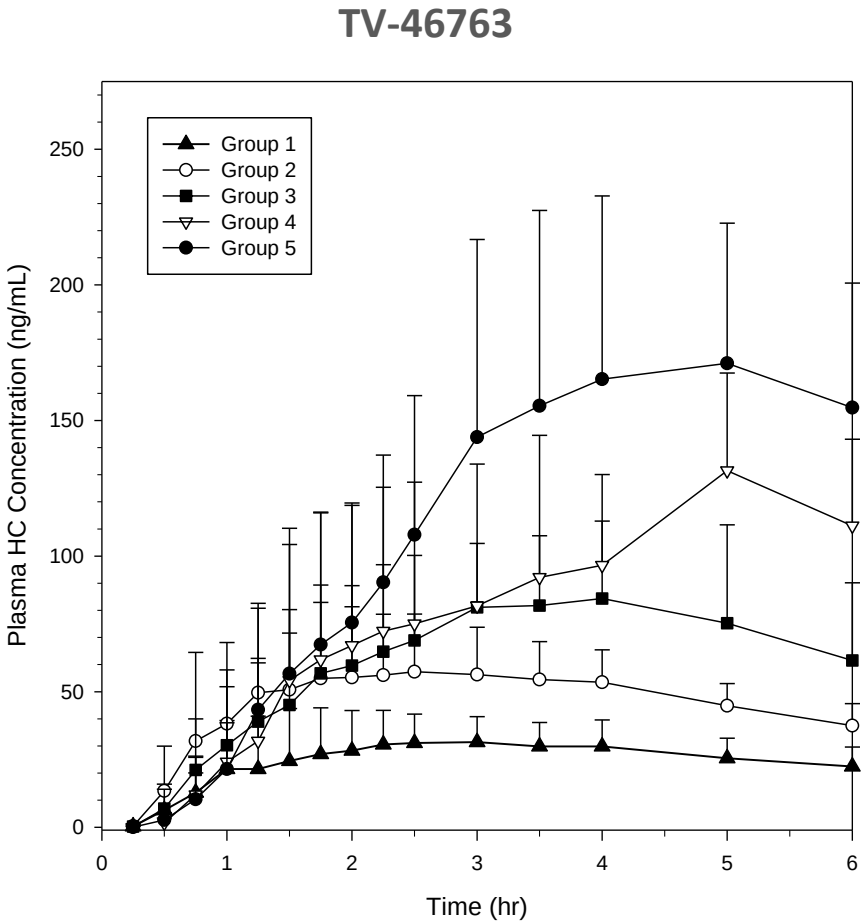
Parameter	Norco						TV-46763					
	2 tablet (n=8)	4 tablet (n=8)	6 tablet (n=8)	8 tablet (n=9)	10 tablet (n=8)	Ratio for 10:2 tablets	2 tablet (n=8)	4 tablet (n=8)	6 tablet (n=10)	8 tablet (n=10)	10 tablet (n=8)	Ratio for 10:2 tablets
C_{max} (ng/mL)	47.68 (17.34)	74.13 (17.28)	154.99 (55.49)	165.73 (36.09)	213.62 (50.44)	4.5	35.35 (13.55)	70.12 (22.41)	97.85 (31.73)	143.30 (35.82)	189.66 (55.11)	5.4
$T_{max\ (hr)}$**	1.3 (0.5, 4.0)	1.1 (0.75, 2.0)	1.0 (0.75,3.0)	1.8 (1.0, 3.0)	1.3 (0.75, 2.0)	Similar	2.5 (1.5, 4.0)	2.4 (1.25, 5.0)	3.3 (0.75,5.0)	5.0 (1.5,5.0)	4.0 (3.0, 8.0)	delayed
AUC_{0-1} (hr*ng/mL)	19.51 (13.16)	29.05 (18.40)	65.58 (36.84)	46.43 (25.79)	91.64 (56.51)	4.7	7.27 (8.02)	16.20 (16.01)	10.88 (9.71)	6.42 (7.28)	5.98 (5.04)	0.8
AUC_{0-2} (hr*ng/mL)	57.7 (25.9)	90.0 (26.9)	183.33 (79.48)	192.90 (62.24)	285.80 (96.27)	5.0	31.5 (25.8)	66.7 (42.6)	57.33 (30.60)	54.77 (49.39)	59.96 (45.38)	1.9
AUC_{0-6} (hr*ng/mL)	162 (51)	262 (52)	546.41 (201.07)	670.93 (122.95)	863.64 (189.74)	5.3	144 (58)	268 (79)	357.56 (107.04)	455.80 (141.72)	654.47 (241.13)	4.5
AUC_{0-t} (hr*ng/mL)	278 (99)	439 (95)	919.99 (330.37)	1226.14 (274.45)	1448.21 (295.43)	5.2	276 (109)	514 (117)	732.14 (269.01)	1152.53 (229.56)	1645.47 (452.58)	6.0

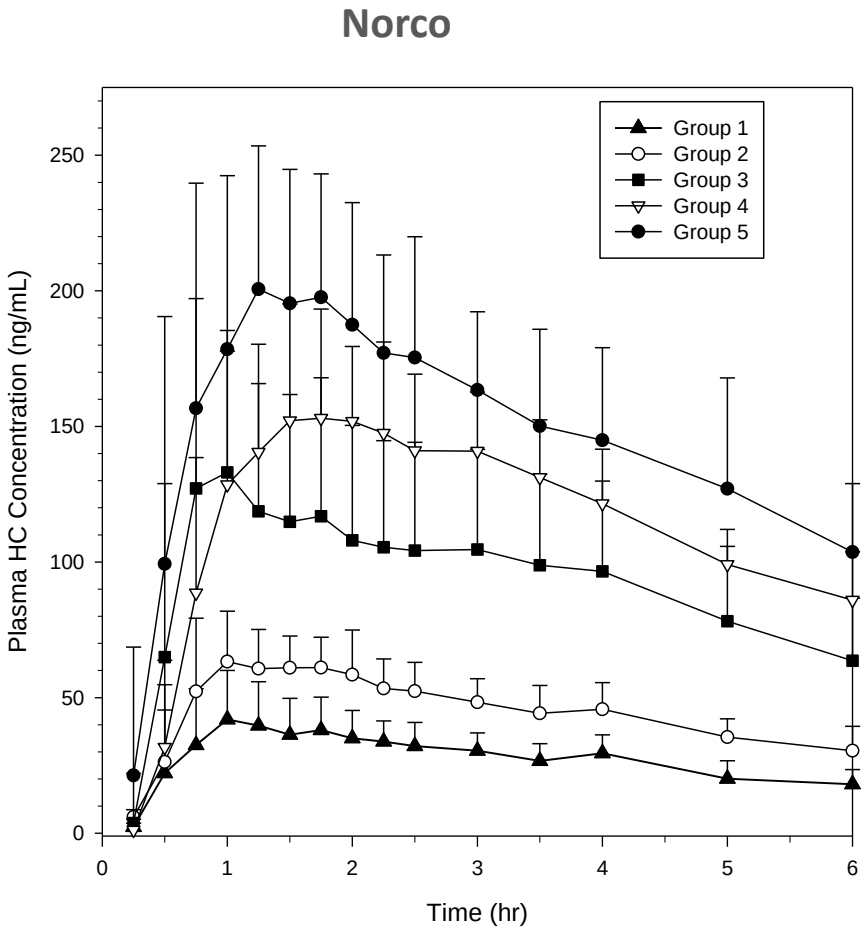
* presented when relevant

** Tmax presented as median (range)

Note: Dose proportionality not formally tested; based on preliminary non-QC'd parameter data

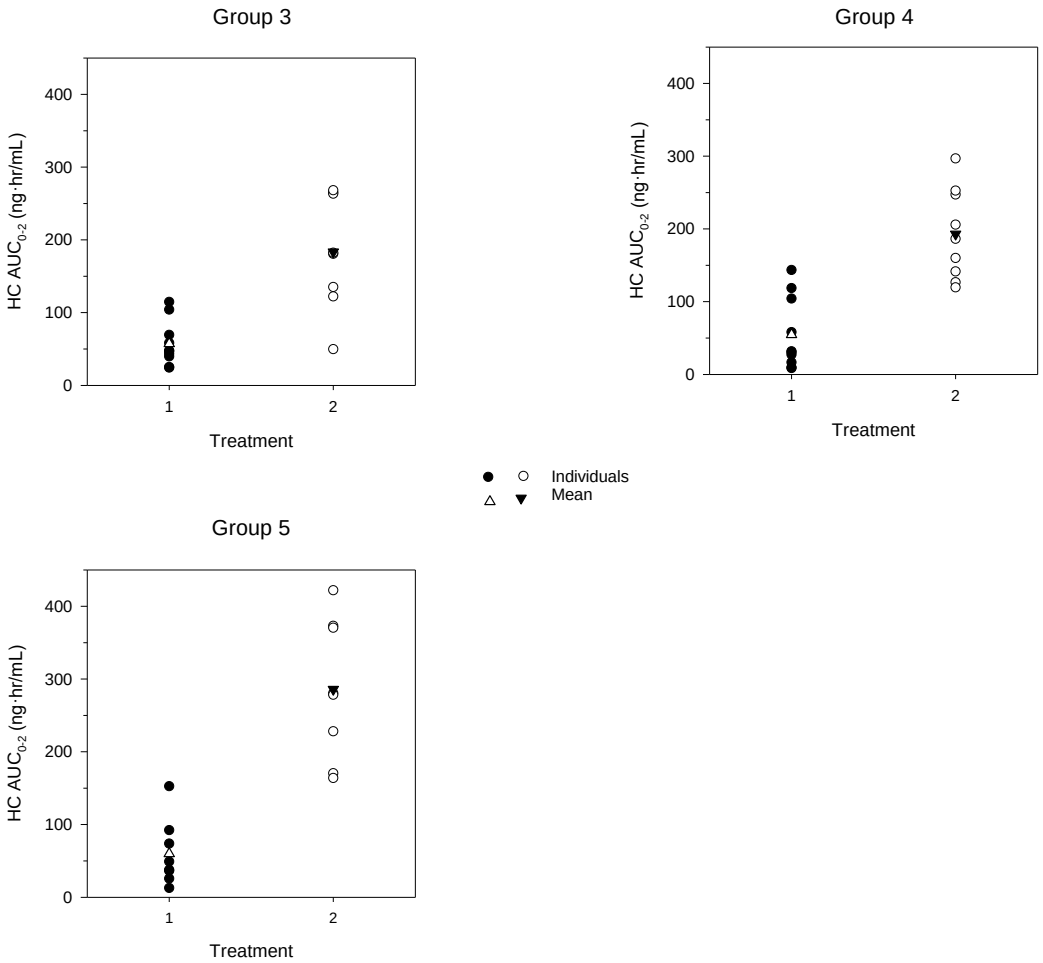
HC Concentration-Time Profiles (10028)





Group 1=2 tablets, Group 2=4 tablets, Group 3=6 tablets, Group 4=8 tablets, Group 5=10 tablets

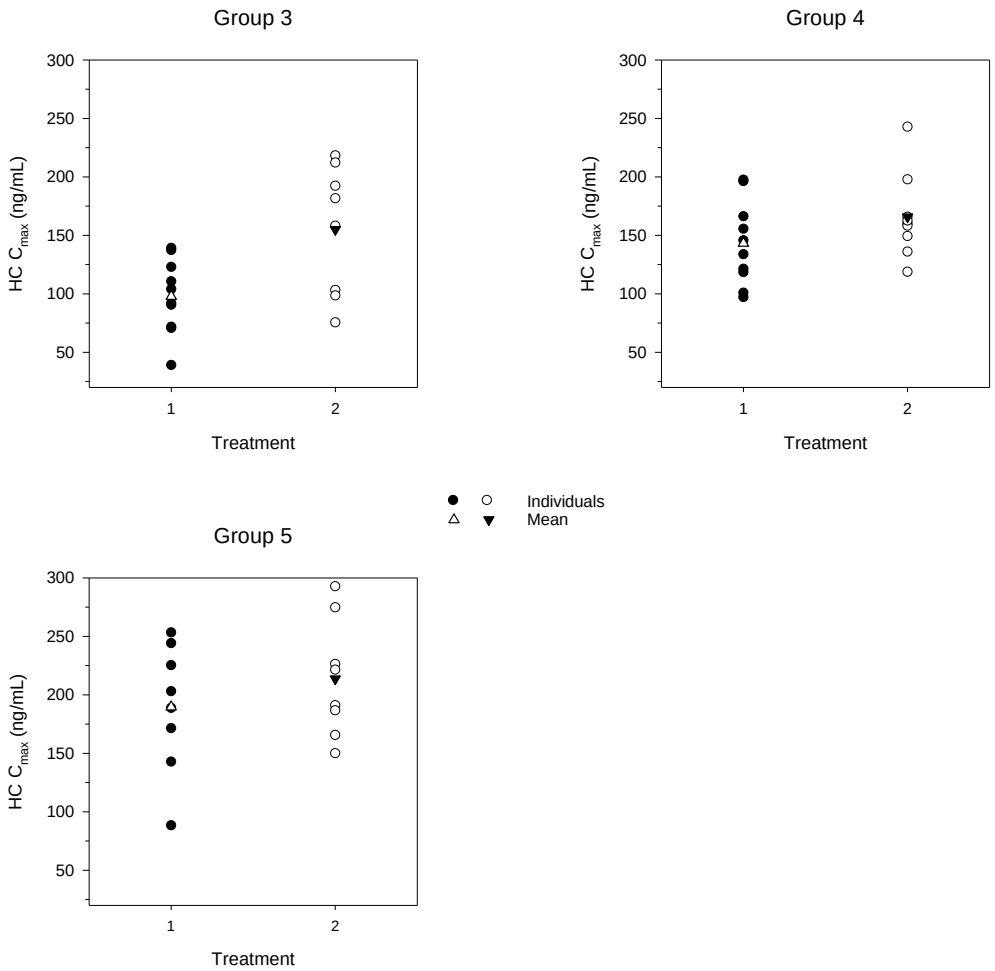
Hydrocodone AUC_{0-2} by treatment & dose (10028)



Group 3=6 tablets, Group 4=8 tablets, Group 5=10 tablets

Treatment 1 = TV-46763 and Treatment 2=Norco

Hydrocodone C_{max} by treatment and Dose (10028)



Group 3=6 tablets, Group 4=8 tablets, Group 5=10 tablets
Treatment 1 = TV-46763 and Treatment 2=Norco

APAP PK Parameters (10028)

Mean (SD*) Pharmacokinetic APAP Parameters following Administration of TV-46763 and Norco

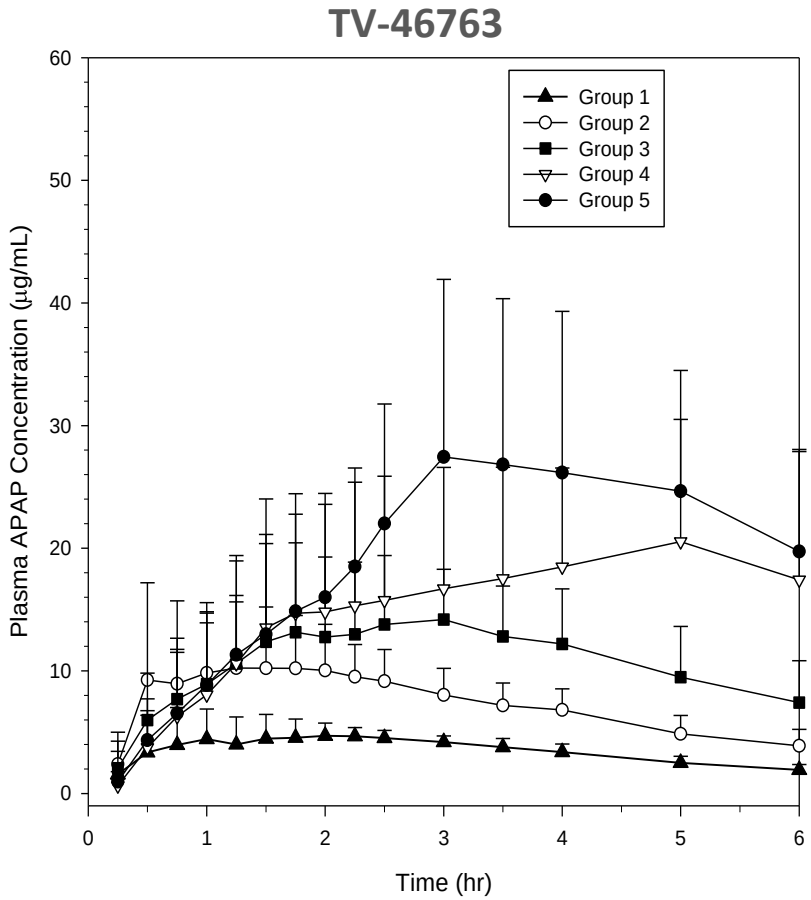
Parameter	Norco						TV-46763					
	2 tablet (n=8)	4 tablet (n=8)	6 tablet (n=8)	8 tablet (n=9)	10 tablet (n=8)	Ratio for 10:2 tablets	2 tablet (n=8)	4 tablet (n=8)	6 tablet (n=10)	8 tablet (n=10)	10 tablet (n=8)	Ratio for 10:2 tablets
C_{max} (µg/mL)	7.90 (2.44)	13.91 (6.21)	23.06 (7.09)	28.43 (6.15)	41.44 (14.58)	5.2	6.05 (1.63)	13.09 (5.41)	17.82 (5.53)	27.68 (9.01)	31.21 (11.09)	5.2
$T_{max\ (hr)}$**	0.8 (0.75, 1.75)	1.1 (0.25, 1.75)	0.8 (0.25, 2.5)	1.3 (0.75, 2.5)	1.0 (0.25, 2.0)	similar	2.1 (0.5, 3.5)	1.1 (0.5, 4.0)	2.1 (0.75, 4.0)	3.8 (1.5, 6.0)	3.0 (1.25, 5.0)	delayed
AUC_{0-1} (hr*µg/mL)	4.78 (2.13)	7.11 (4.57)	13.58 (6.57)	13.05 (5.77)	25.09 (14.92)	5.2	2.72 (2.28)	6.39 (4.82)	5.05 (3.91)	3.67 (2.96)	4.07 (2.89)	1.5
AUC_{0-2} (hr*µg/mL)	10.40 (3.20)	17.16 (5.63)	31.16 (13.69)	35.88 (8.58)	57.77 (22.33)	5.6	7.06 (4.04)	16.53 (9.02)	16.79 (8.27)	16.23 (11.00)	16.96 (10.07)	2.4
AUC_{0-6} (hr*µg/mL)	22.3 (3.6)	40.6 (8.6)	75.80 (26.67)	103.42 (17.52)	142.66 (35.70)	6.4	20.5 (4.9)	43.1 (15.4)	62.62 (18.34)	88.03 (30.37)	113.10 (43.47)	5.5
AUC_{0-t} (hr*µg/mL)	29.0 (4.7)	56.8 (13.8)	102.31 (35.64)	149.89 (38.47)	194.83 (47.54)	6.7	29.5 (7.6)	61.4 (20.7)	94.43 (29.53)	166.50 (67.93)	210.75 (91.97)	7.1

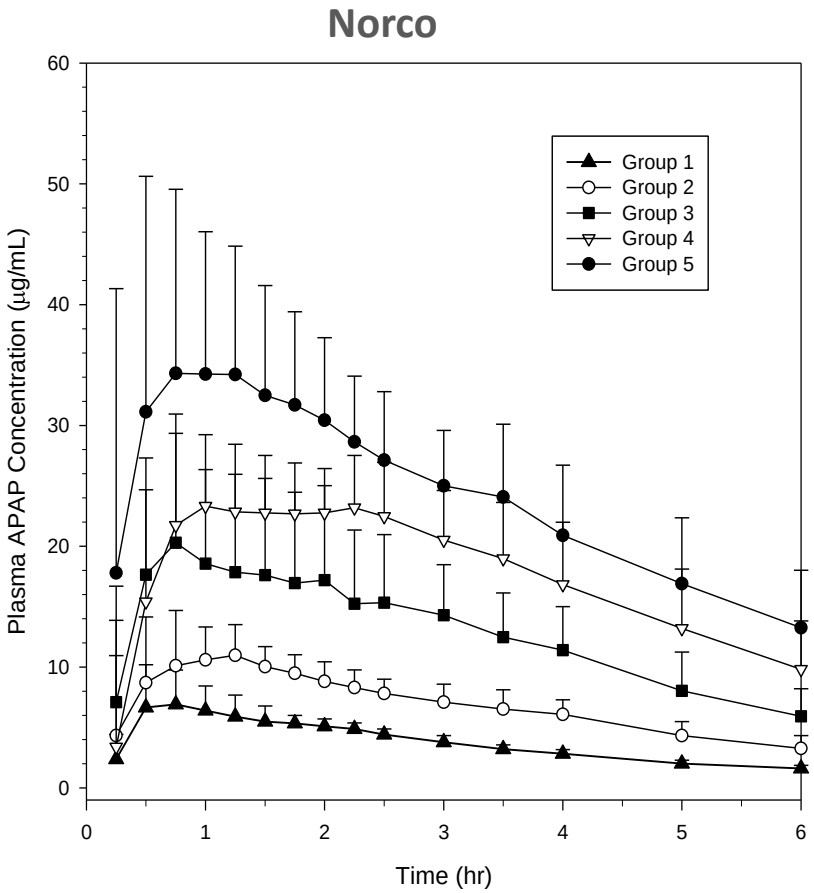
* presented when relevant

** Tmax presented as median (range)

Note: Dose proportionality not formally tested; based on preliminary non-QC'd parameter data

APAP Concentration-Time Profiles (10028)





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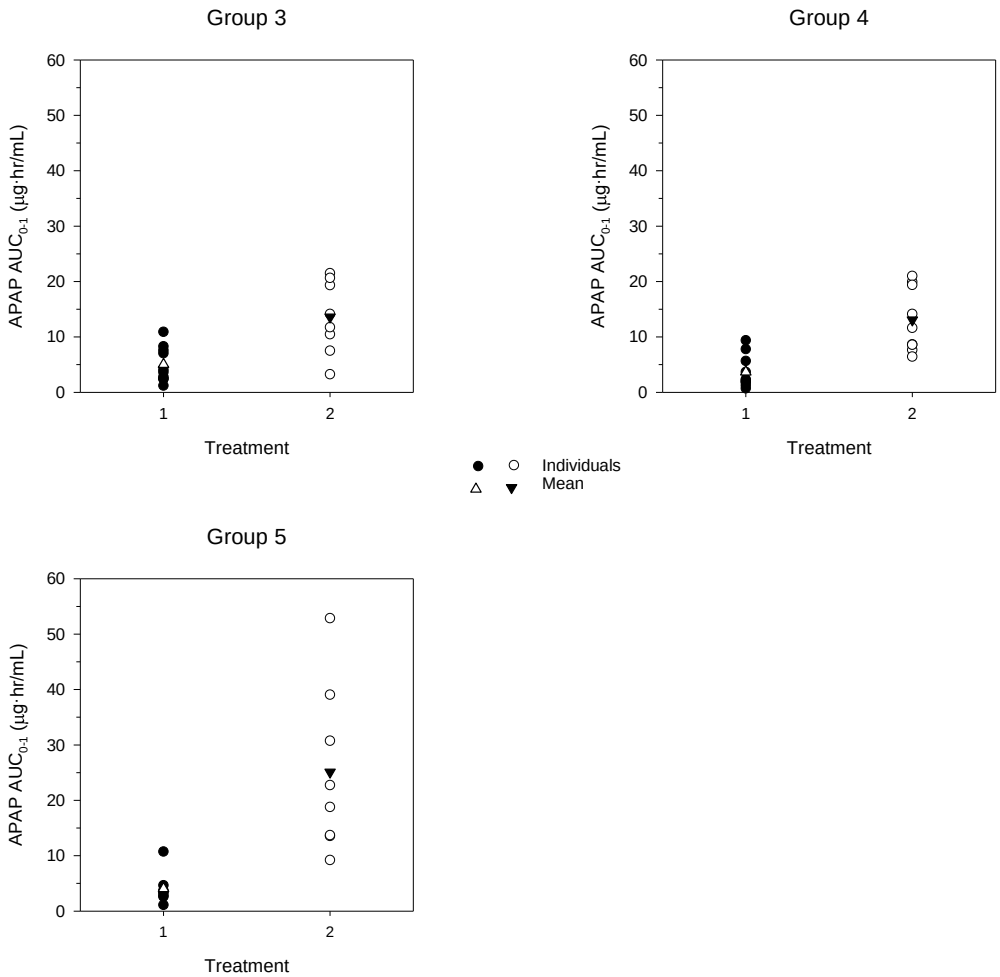
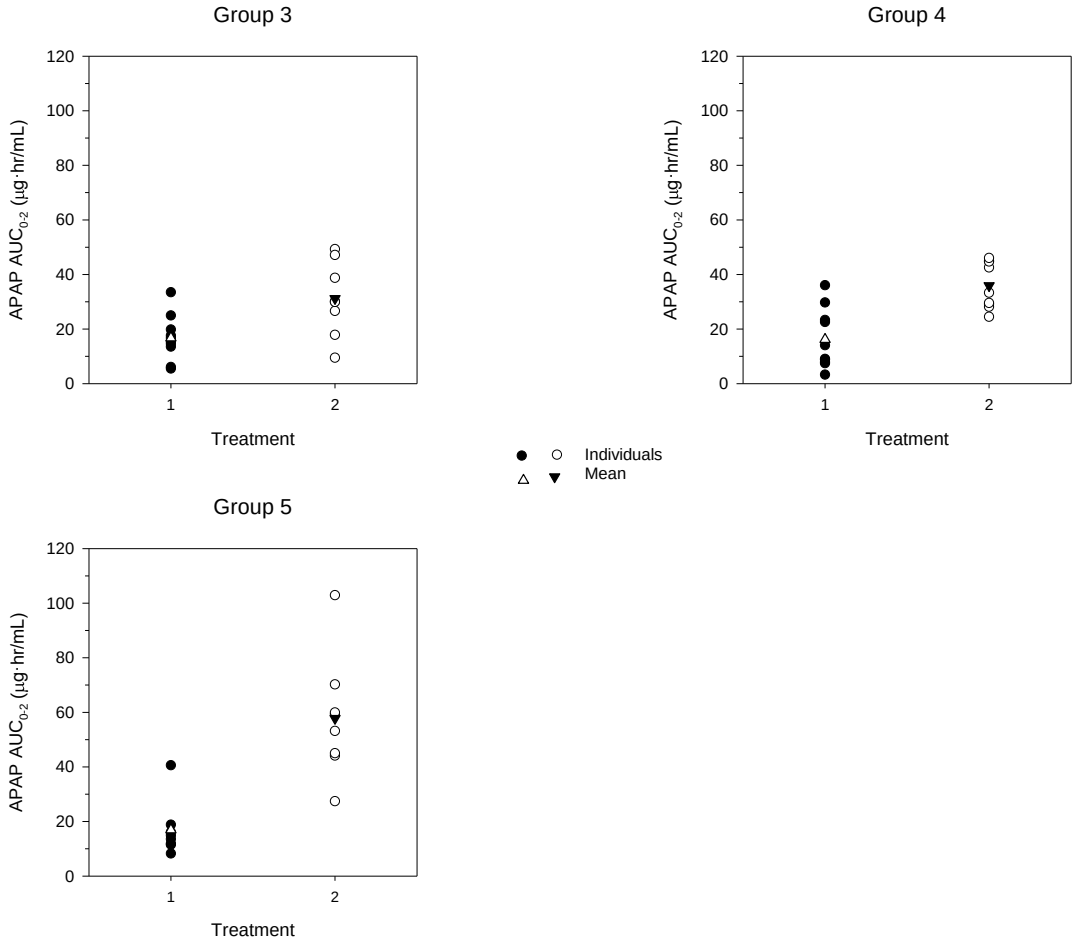
APAP AUC_{0-1} by treatment & dose (10028)



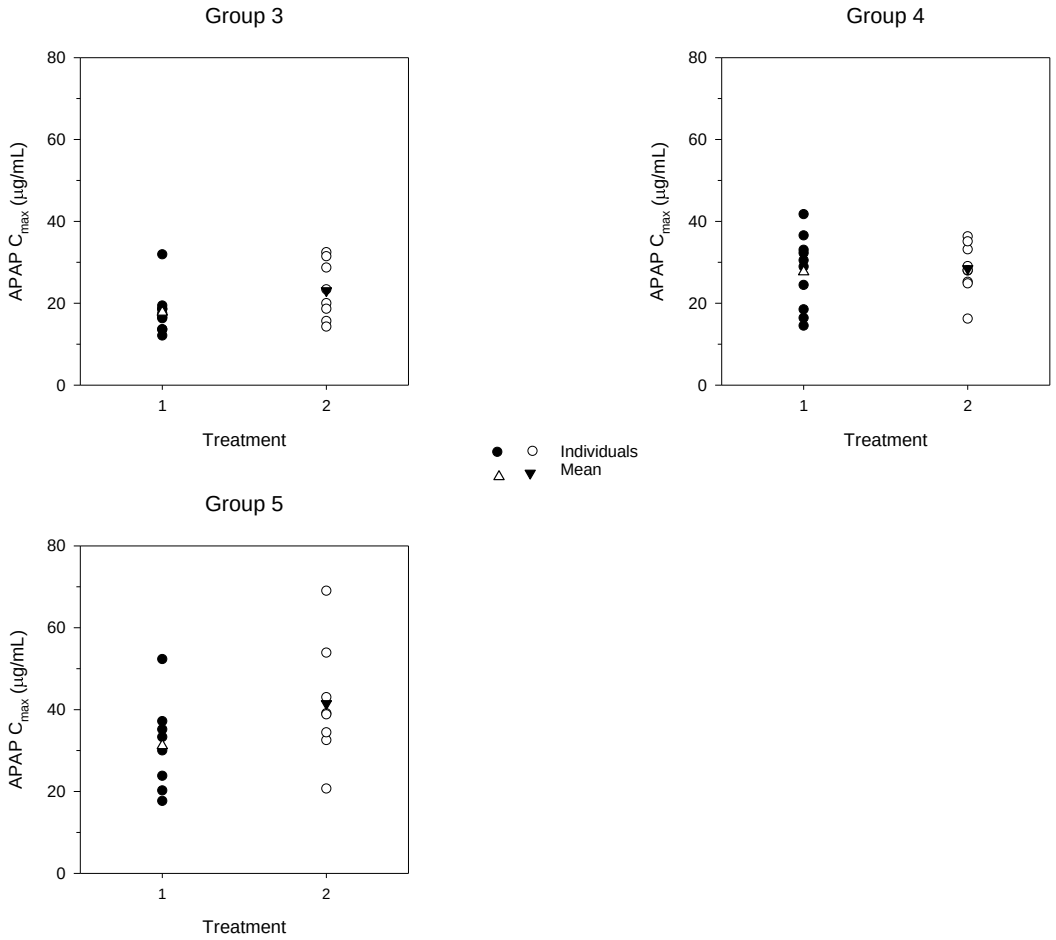
Group 3=6 tablets, Group 4=8 tablets, Group 5=10 tablets
Treatment 1 = TV-46763 and Treatment 2=Norco

APAP AUC_{0-2} by treatment & Dose (10028)



Group 3=6 tablets, Group 4=8 tablets, Group 5=10 tablets
Treatment 1 = TV-46763 and Treatment 2=Norco

APAP C_{max} by treatment & Dose (10028)



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Treatment 1 = TV-46763 and Treatment 2=Norco