

FDA ADVISORY COMMITTEE BRIEFING DOCUMENT

Xtampza™ ER (EXTENDED-RELEASE OXYCODONE)

**JOINT MEETING OF THE ANESTHETIC AND ANALGESIC
DRUG PRODUCTS ADVISORY COMMITTEE AND THE DRUG
SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE**

MEETING DATE: September 11, 2015

Available for Public Release

Table of Contents

1	Executive Summary.....	10
1.1	Unmet Medical Need in the Treatment of Pain Requiring Around-the-Clock Opioid Treatment.....	11
1.2	Abuse Deterrence Evaluation	12
1.3	Food and Alcohol Effects	15
1.3.1	Effects of Food on Xstampza ER.....	15
1.3.2	Effects of Alcohol on Xstampza ER	18
1.3.3	PK of Sprinkling Xstampza ER onto Soft Foods or Directly into the Mouth	18
1.4	Efficacy Findings in Phase 3 Study	19
1.5	Safety Findings in the Phase 3 Study	20
1.6	Benefit/Risk Assessment	20
2	Unmet Medical Need in Treatment of Pain Requiring Around-the-Clock Opioid Treatment	22
2.1	Background on Chronic Pain.....	22
2.2	Abuse of Extended-Release Opioid Products.....	23
2.3	Unmet Medical Need in Patients Requiring Opioid Treatment Who Have Difficulty Swallowing	23
3	Overview of Xstampza ER Formulation and Development Program.....	26
3.1	Product Characteristics	26
3.2	Key FDA Milestones and Guidance During Development	27
3.3	Overview of Abuse-Deterrence Evaluation.....	28
3.3.1	Category 1 Studies – In Vitro Manipulation and Extraction Studies	28
3.3.2	Category 2 Studies – Pharmacokinetics	28
3.3.3	Category 3 Studies – Human Abuse Potential	29
3.4	Relative Bioavailability and Food- and Alcohol-Effect Studies	29
3.5	Dosage and Administration Studies.....	30
3.6	Phase 3 Safety, Tolerability and Efficacy Clinical Study.....	30
4	Abuse Deterrent Evaluation	32
4.1	Category 1: In Vitro Manipulation and Extraction.....	33
4.1.1	Particle Size Reduction Studies.....	33
4.1.2	Optimization Study for Method A.....	34
4.1.3	Heat and Freeze PSR Study.....	35

4.1.4	Chemical Manipulation	35
4.1.5	Route Specific Method of Abuse: IV Injection.....	37
4.1.6	Route Specific Method of Abuse: Smoking.....	39
4.2	Category 2: Pharmacokinetics	41
4.2.1	Oral Administration of Manipulated Xtampza ER – Study 17	41
4.2.2	Oral Administration of Chewed Xtampza ER – Study 24	42
4.2.3	Oral Administration of Manipulated Xtampza ER versus OxyContin ADF – Study 25.....	43
4.2.4	Nasal Administration of Manipulated Xtampza ER – Study 21	45
4.2.5	Nasal Administration of Manipulated Xtampza ER – Study 19	47
4.3	Category 3: Human Abuse Potential	47
4.3.1	General Methodology	47
4.3.2	Nasal Human Abuse Potential Study – Study 21	48
4.3.3	Oral Human Abuse Potential Study – Study 24	50
4.4	Abuse Deterrence Evaluation Conclusions	51
5	Food and Alcohol Effects	52
5.1	Approach to Assessing the Effect of Food on Xtampza ER.....	53
5.2	Pharmacokinetic Evaluation of the Food Effect	53
5.2.1	Introduction to Relative Bioavailability and Food Effect Studies.....	53
5.2.2	Single-Dose, NTX-Blocked Study – Study 15.....	55
5.2.3	Steady State, NTX-Blocked Study – Study 18.....	58
5.2.4	Single-Dose, Non-NTX-Blocked Study – Study 24.....	60
5.2.5	Individual Subject C_{max} Ratios Comparing Fed-to-Fasted Administration.....	61
5.2.6	Food Effects in Other Opioid Products	61
5.3	Evaluation of Influence of Food in the Phase 3 Safety and Efficacy Study.....	62
5.3.1	Safety and Food Intake at Dosing	62
5.3.2	Efficacy and Food Intake at Dosing	64
5.4	Conclusions Regarding Studies Characterizing Food Effect of Xtampza ER.....	64
5.5	Effect of Alcohol on Bioavailability of Xtampza ER – Study 26	65
6	Alternative Methods of Drug Administration.....	66
6.1	PK During Sprinkling onto Soft Food	66
6.2	In Vitro Dissolution for Other Soft Foods	67
6.3	In Vitro Studies of Dosing Via Nasogastric/Gastrostomy Tubes	68
7	Clinical Efficacy in Phase 3 Study.....	70
7.1	Study Design.....	70

7.1.1	Procedures and Assessments	71
7.1.2	Clinical Endpoints	72
7.1.3	Analysis Populations	73
7.2	Statistical Methodology	73
7.3	Subject Disposition.....	74
7.4	Demographics and Baseline Characteristics.....	75
7.5	Primary Endpoint Results	76
7.5.1	Consistency of Findings across Subgroups	77
7.6	Key Secondary Endpoints.....	77
7.6.1	Responder Analysis for Pain Intensity at Week 12	77
7.6.2	All-Cause Time-to-Exit from Study	78
7.6.3	Patient Global Impression of Change (PGIC)	78
8	Clinical Safety in Phase 1 and Phase 3 Studies	79
8.1	Summary of Safety in Phase 1	79
8.2	Ascertainment of Phase 3 Safety Data.....	79
8.3	Safety in Phase 3 Study	80
8.3.1	Adverse Event Summary	80
8.3.2	Adverse Events Leading to Study Drug Termination	81
8.3.3	Deaths	81
8.3.4	Nonfatal Serious Adverse Events	81
9	Post-Marketing Risk Assessment and Management	83
10	Benefit-Risk Assessment	85
10.1	Class-wide Risks of Opioids.....	85
10.2	Benefits of the Novel Xtampza ER Microsphere Formulation	85
10.3	Food Effect of Xtampza ER	87
10.4	Overall Conclusion	88
11	Reference List.....	89
12	Appendix.....	92
12.1	Meal Pattern Safety Analysis Tables	92

List of Tables

Table 1:	Limitations of Currently Marketed Opioid Formulations	24
Table 2:	Xtampza ER Dosage Strengths.....	27
Table 3:	Overview of Category 2 Studies.....	28
Table 4:	Overview of Category 3 Studies.....	29
Table 5:	Overview of Food- and Alcohol-Effect Studies	30
Table 6:	Overview of Clinical Dosage and Administration Study	30
Table 7:	Category 1 Abuse-Deterrent Studies	33
Table 8:	Average Percent of Drug Extracted from Crushed Xtampza ER vs Crushed OxyContin ADF and IR Oxycodone at Room Temperature with Continuous Agitation	36
Table 9:	Average Percent of Drug Extracted Following Secondary Extraction for Crushed Xtampza ER, OxyContin ADF, and IR oxycodone	37
Table 10:	Studies Assessing Relative Bioavailability and Food Effect.....	54
Table 11:	Bioavailability of Xtampza ER with Food Relative to OxyContin ADF – Study 15	56
Table 12:	Summary of PK Parameters for Xtampza ER and OxyContin ADF, Steady-State Fed Dosing – Study 18	58
Table 13:	Dosing Meal Pattern Analysis Summary.....	64
Table 14:	Summary of 24-Hour Pain Scores throughout the Phase 3 Study by Meal Pattern.....	64
Table 15:	Demographic and Baseline Characteristics – Study 08 (ITT Population).....	75
Table 16:	Primary, Secondary, and Sensitivity Analyses of the Primary Endpoint	77
Table 17:	Overview of Adverse Events During the Double-blind Maintenance Phase – Study 08 (Randomized Safety Population).....	80
Table 18:	Summary of Most Common Adverse Events with a Frequency $\geq 3\%$ in the Xtampza ER Group during Double-blind Maintenance Phase – Study 08 (Randomized Safety Population).....	81
Table 19:	Summary of AE Rates by Prior Day Meal Pattern	92
Table 20:	Summary of AE Rates by Prior PM Meal and Current AM Meal Pattern	92
Table 21:	Summary of AE Rates by Current Day Meal Pattern	93

List of Figures

Figure 1: Xtampza ER Microsphere Formulation.....	10
Figure 2: Mean Oxycodone Concentration over Time – Study 25	14
Figure 3: Oxycodone Concentration under Fasted/Fed Dosing Administration at Day 5 – Study 18	16
Figure 4: Bioequivalence Parameters for Fasted versus Fed Dosing with Xtampza ER with and without NTX Block – Studies 15 and 24.....	17
Figure 5: Oxycodone Concentration following Xtampza ER Administration Intact and Sprinkled onto Applesauce under Fed Conditions – Study 27	19
Figure 6: Primary and Sensitivity Analyses of the Primary Endpoint in the Phase 3 Study	20
Figure 7: Impact of Most Effective Manipulation Tools on Drug Release for Xtampza ER and OxyContin ADF.....	34
Figure 8: Extraction Following Crushing and Exposure to Water at Boiling Point	38
Figure 9: Extraction Following Crushing, Pretreatment A, and Exposure to Water at Boiling Point.....	39
Figure 10: Mass (mg) Oxycodone Recovered in Vapor	40
Figure 11: Mean C _{max} Values under Fed Conditions – Study 17	41
Figure 12: Mean Oxycodone Partial AUC Values – Study 17	42
Figure 13: Mean C _{max} Values – Study 24.....	43
Figure 14: Mean Plasma Oxycodone Concentrations – Study 25.....	44
Figure 15: Mean Plasma Oxycodone Concentration through 2 Hours – Study 25	44
Figure 16: Abuse Quotient Values – Study 25.....	45
Figure 17: Mean C _{max} Values – Study 21.....	46
Figure 18: Mean Partial AUC Values – Study 21	46
Figure 19: Mean C _{max} Values – Study 19.....	47
Figure 20: Maximum Drug Liking (E _{max}) – Study 21	49
Figure 21: Percentage Reduction Profile for E _{max} of Drug Liking VAS for Crushed Xtampza IN versus Crushed IR Oxycodone IN – Study 21	49
Figure 22: Maximum Drug Liking (E _{max}) – Study 24.....	50
Figure 23: Percent Reduction Profiles for E _{max} of Drug Liking VAS for Chewed and Intact Xtampza ER versus Crushed IR Oxycodone – Study 24	51

Figure 24: Bioequivalence Parameters for Xtampza ER Relative to OxyContin ADF under Fed (HFHC) and Fasted Conditions, Single-Dose with NTX Block – Study 15	55
Figure 25: Bioequivalence Parameters for Xtampza ER and OxyContin ADF for Fasted to Fed (HFHC) States, Single-Dose with NTX Block – Study 15	57
Figure 26: Mean Concentrations of Oxycodone After Fed and Fasting Dosing – Study 18	59
Figure 27: Steady-State Percent Peak-Trough Fluctuations, Alternating Fasted and Fed Dosing – Study 18	60
Figure 28: Effect of Food on Xtampza ER Bioavailability with and without Naltrexone	60
Figure 29: PK Characteristics of Food Effects of FDA-Approved Opioids and Xtampza ER	62
Figure 30: Mean Peak Oxycodone Concentration with Xtampza ER 40 mg – Study 26	65
Figure 31: Oxycodone Concentration following Xtampza ER Administration Intact and Sprinkled onto Applesauce under Fed Conditions – Study 27	67
Figure 32: Xtampza ER Dissolution Profile Intact and Sprinkled on Various Soft Foods	68
Figure 33: Xtampza ER Dissolution Profile Intact and Passed through Feeding Tubes Using a Water Delivery Vehicle	69
Figure 34: Design of Phase 3 Study	71
Figure 35: Subject Disposition – Study 08.....	75

List of Abbreviations and Definition of Terms

AE	adverse event
ANCOVA	analysis of covariance
APAP	acetaminophen
API	active pharmaceutical ingredient
AQ	abuse quotient
ARCI/MBG	Addiction Research Center Inventory/Morphine Benzedrine Group
BA	bioavailability
BE	bioequivalence/bioequivalent
BOCF	baseline observation carried forward
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CLBP	chronic low back pain
COWS	Clinical Opiate Withdrawal Scale
CPD	chronic pain with dysphagia
DEA	Drug Enforcement Administration
DEQ	Drug Effects Questionnaire
ECG	electrocardiogram
E _{max}	maximum effect
ER	extended-release
f ₂	similarity factor
FDA	United States Food and Drug Administration
G	gastrostomy
GERD	gastroesophageal reflux disease
GM	geometric mean
GRAS	generally recognized as safe
HAP	human abuse potential
HCl	hydrochloride
HFHC	high-fat, high-calorie

List of Abbreviations and Definition of Terms

IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IN	intranasal
IR	immediate-release
ITT	intent-to-treat
IV	intravenous
LA	long-acting
LFLC	low-fat, low-calorie
LS	least squares
LOCF	last observation carried forward
MFMC	medium-fat, medium-calorie
MMRM	mixed effects model for repeated measures
MSE	morphine sulfate equivalent
NDA	New Drug Application
NG	nasogastric
NTX	naltrexone
NSAID	nonsteroidal anti-inflammatory drug
PAUC	partial area under the curve
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PI-NRS	Pain Intensity-Numerical Rating Scale
PK	pharmacokinetic(s)
PMR	Post-Marketing Requirement
PSR	particle size reduction
PTF	peak-trough fluctuation
REMS	Risk Evaluation and Mitigation Strategy
RPC	REMS Program Companies
SD	standard deviation
VAS	visual analog scale

1 EXECUTIVE SUMMARY

Xtampza ER is an extended-release (ER) capsule formulation of oxycodone with a proposed indication to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Collegium Pharmaceutical, Inc. (herein “Collegium”) submitted a New Drug Application (NDA) to the Food and Drug Administration (FDA) requesting approval of Xtampza ER on December 12, 2014.

Xtampza ER is an abuse-deterrent, microsphere-in-capsule formulation (Figure 1). Each microsphere is both ER and provides resistance to manipulations that may be attempted by abusers to defeat the ER properties of the product. In each microsphere, oxycodone is present as a solid solution of a fatty acid salt (oxycodone myristate) in a hydrophobic matrix that also contains waxes. Homogeneous dispersion of the active pharmaceutical ingredient (API) in the form of a solid solution in fatty acid and waxes impart the drug’s ER properties. The small particle size (median size ~300 microns) and waxy, hydrophobic nature also contribute to Xtampza ER’s abuse-deterrent features.

If approved by the FDA, Xtampza ER will be provided in dosage strengths that contain oxycodone in an amount equivalent to 10, 15, 20, 30, or 40 mg of oxycodone hydrochloride (HCl). The proposed labeling recommends that Xtampza ER should be administered with food because the full release of the drug from the formulation is achieved in the presence of food.

During development, FDA provided significant input, particularly in design of the studies to evaluate abuse potential. In the FDA Guidance, these studies are referred to as Category 1 (in vitro laboratory physical and chemical manipulation), Category 2 (pharmacokinetic [PK]) and Category 3 (human abuse potential [HAP]). While these studies were conducted based upon an earlier draft FDA Guidance ([CDER, 2013](#)), the overall study designs are consistent with the final FDA Guidance for the development of opioid abuse-deterrent formulations (ADFs) ([CDER, 2015a](#)).

Figure 1: Xtampza ER Microsphere Formulation



Xtampza ER microspheres were designed to address three key issues affecting both patient care and public health:

- **Unintentional misuse.** *Patients should not crush or chew currently marketed ER opioids, which can destroy the ER delivery system and cause life-threatening adverse events.*

Development studies demonstrated that crushing or chewing Xtampza ER did not compromise its ER properties. Administration of Xtampza ER, whether crushed or chewed, did not increase either maximum drug exposure (C_{max}) or total exposure (AUC) relative to dosing the drug intact as a capsule, or result in “dose dumping”, which would put a patient at significant risk.

- **Unmet need for patients with difficulty swallowing.** *“Hard-to-crush” abuse-deterrant ER opioids are either difficult or impossible for many patients with dysphagia to swallow.*

For patients who have difficulty swallowing, Xtampza ER may be administered by sprinkling the capsule contents onto soft foods or directly into the mouth. In vitro studies have also shown that Xtampza ER may be administered directly through a feeding tube without changing the release properties. There are no currently available abuse-deterrant products on the market with those similar benefits.

- **Intentional abuse.** *ER opioids are physically manipulated and/or extracted for oral, nasal, and intravenous (IV) abuse.*

The Xtampza ER formulation provides resistance to common manipulations used by abusers to overcome the time-release mechanism of ER dosage forms. Direct injection and extraction studies showed that Xtampza ER microspheres provide resistance to IV injection, with less drug extracted in injectable volumes of water when compared with reformulated OxyContin (herein “OxyContin ADF”). The ER properties of Xtampza ER are not compromised when crushed, unlike OxyContin ADF, which becomes bioequivalent to IR oxycodone after crushing. Crushing and snorting Xtampza ER for the purposes of nasal abuse results in lower peak oxycodone exposure than when administered orally, intact, as a capsule as intended per the proposed label. Finally, nasal and oral HAP studies found that the drug liking of manipulated Xtampza ER among recreational opioid abusers was significantly lower than IR oxycodone.

1.1 Unmet Medical Need in the Treatment of Pain Requiring Around-the-Clock Opioid Treatment

Chronic pain is a serious condition afflicting millions of Americans (Johannes et al., 2010; Pergolizzi et al., 2008; American Academy of Pain Medicine, 2013). Chronic pain is often treated with ER opioids and co-prescribed with a short-acting opioid to treat breakthrough pain. An estimated 4 million Americans take opioids regularly (i.e., at least 5 days per week for at least 4 weeks) (Parsells et al., 2008).

Escalating medical use of opioids has correlated with an increase in the incidence of opioid-related drug abuse ([Maxwell, 2011](#)). Opioids are often manipulated to transform conventional ER dosage forms to IR forms for the purposes of abuse by the oral, nasal, or IV routes of administration. Patients, caregivers, and health professionals may also misuse ER opioids by crushing or chewing, which can lead to life-threatening adverse events AEs.

In an effort to combat this type of product manipulation, opioid ADFs have been and are being developed, such as opioid formulations combined with an antagonist, formulations with aversive characteristics, or those possessing physical and/or chemical characteristics that decrease the effectiveness of tampering. In 2010, Purdue Pharma L.P. (Stamford, CT) introduced a reformulated version of OxyContin ER tablets, OxyContin ADF, which are produced via a manufacturing process that results in a relatively hard tablet that is more difficult to crush than the original formulation. Its introduction has resulted in a decrease in abuse of OxyContin compared with the original formulation, however the tablets remain susceptible to relatively simple physical manipulations that compromise the time-release.

An unintended consequence of the reformulation of OxyContin ADF and other hard-tablet opioid formulations containing gelling polymers is that the tablets can be difficult for some patients to swallow. In fact, the prescribing information for OxyContin ADF describes post-marketing reports of choking, gagging, regurgitation, and tablets stuck in the throat ([Purdue Pharma L.P., 2014](#)). FDA has recognized that difficulties swallowing pills is a common issue that may go well beyond patients with clinically-recognized dysphagia, affecting as many as 40% of the United States (US) population ([CDER, 2015c](#)). Consistent with the FDA Guidance, a large survey of patients taking opioids for chronic pain recently found that 29% of patients reported either difficulty swallowing pills or a dislike for swallowing pills ([Pergolizzi et al., 2013](#)). FDA has highlighted the need for opioids with more flexible dosing options in their Guidance for Industry on Abuse-Deterrent Opioids, acknowledging that certain patient populations require an opioid that can be safely administered in a solution or that can be crushed ([CDER, 2015](#)).

1.2 Abuse Deterrence Evaluation

The abuse-deterrent evaluation of Xtampza ER was conducted according to FDA guidance and with specific advice from the Agency throughout the development program. The evaluation included Category 1 (in vitro manipulation and extraction), Category 2 (PK) and Category 3 (HAP) studies.

Category 1 Studies – Manipulation and Extraction

Results from the Category 1 studies demonstrated that Xtampza ER was more difficult to physically manipulate or extract than OxyContin ADF across all of the most common routes of abuse.

In the physical manipulation studies, 11 common household tools that are frequently used by abusers to manipulate ER opioid products were evaluated for their effectiveness in destroying the drugs' time-release properties (i.e., accelerating the rate of drug release). Of these 11 tools, 4 were able to produce at least a 50% release of the drug at 15 minutes with OxyContin ADF, and none with Xtampza ER. Similarly, 8 tools were able to manipulate the drug to produce a

doubling of the standard rate of drug release at 15 minutes with OxyContin ADF; none of the tools were able to do so with Xtampza ER. The most effective methods identified by Collegium for physical manipulation were confirmed by an external, independent laboratory. An additional in vitro study demonstrated that heating or freezing Xtampza ER before physical manipulation did not increase the most effective tools' ability to accelerate drug release.

Xtampza ER provided improved resistance to chemical extraction following physical manipulation in 7 commonly available, ingestible solvents relative to OxyContin ADF and IR oxycodone tablets. At 15 minutes, the percentage of drug extracted at room temperature following crushing with the most effective method for each drug was >80% for 5 of the 7 solvents with OxyContin ADF, >80% for 6 of the solvents with IR oxycodone, and <20% with Xtampza ER for all 7 solvents.

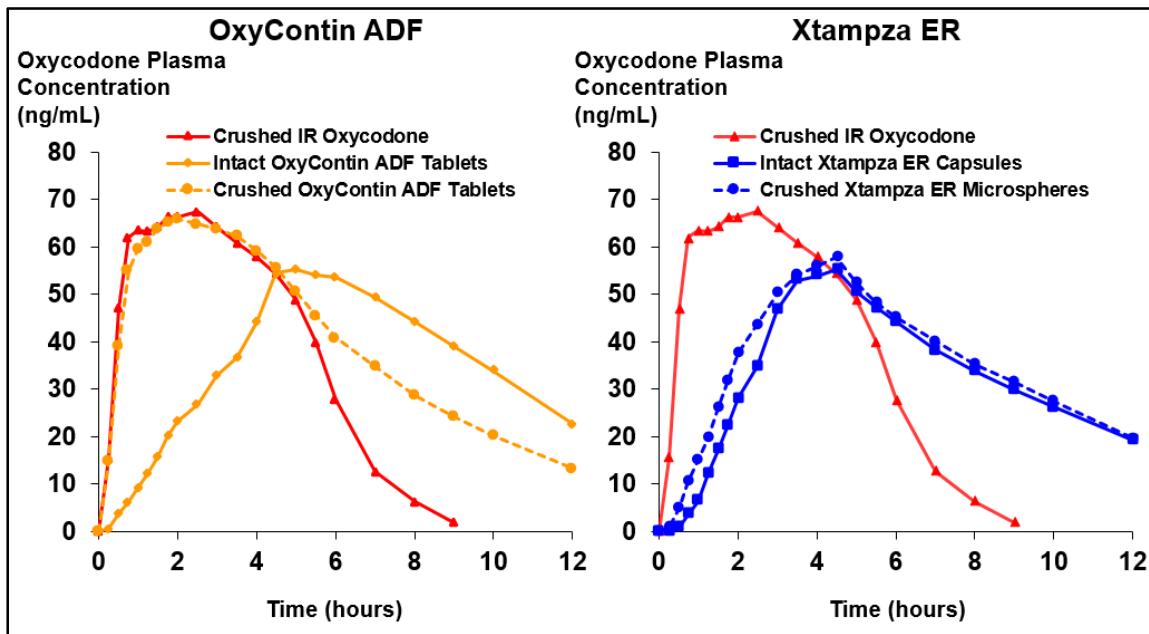
Xtampza ER also provided resistance to manipulations intended to prepare the microspheres for IV injection. Recovery of oxycodone following crushing and extraction in small volumes of water for injection was lower for Xtampza ER than either OxyContin ADF or IR oxycodone. The size and hydrophobic nature of the microspheres make direct injection ineffective; no microspheres passed through a 27 or 22 gauge needle; only an average of 13% of microspheres passed through the extreme upper range of needle size tested (18 gauge). Attempts to melt Xtampza ER and draw the microspheres into syringes for injection were unsuccessful, as Xtampza ER quickly solidifies and clogs the needle.

While smoking oxycodone-containing products is not a common route of abuse, in vitro studies characterized the potential for abusing Xtampza ER, OxyContin ADF, and IR oxycodone by smoking. Based on the similarity in drug release over the majority of the conditions tested and considering the prevalence of smoking for other available oxycodone containing products, smoking is not anticipated to be a preferred route of administration for Xtampza ER.

Category 2 Studies – PK

Three studies specifically assessed the PK of Xtampza ER and relevant comparators when manipulated for oral or nasal abuse. In addition, the Category 3 oral and nasal HAP studies also collected PK data. The key PK findings from these studies were:

- Crushing and chewing Xtampza ER did not result in an increase in peak (C_{max}) or overall (AUC) plasma exposure when compared with taking the capsules intact.
- Crushing Xtampza ER did not affect the time-release mechanism of the drug, unlike OxyContin ADF whose ER properties were destroyed. The plasma concentration for crushed and intact Xtampza ER were bioequivalent (BE), while the plasma curve for OxyContin ADF when crushed was BE to IR oxycodone (Figure 2).
- Crushed and snorted Xtampza ER resulted in lower C_{max} values than when taken intact orally, and does not produce the rapid, high plasma concentrations that abusers seek for euphoria when manipulating and administering dosage forms by the nasal route.

Figure 2: Mean Oxycodone Concentration over Time – Study 25

Category 3 Studies – Human Abuse Potential

The oral and nasal HAP studies evaluated the drug liking of manipulated Xtampza ER in nondependent, nontolerant, recreational drug abusers. In the nasal HAP study (Study 21), the peak effect of mean Drug Liking (E_{max}) for crushed and snorted Xtampza ER was significantly lower than both crushed and snorted IR oxycodone ($P<0.0001$) and intact oral dosing of Xtampza ER ($P=0.034$). Intact oral dosing of Xtampza ER also produced lower mean Drug Liking than crushed/snorted IR oxycodone ($P<0.0001$). This study suggests a lower abuse potential for both intact oral and crushed intranasal administration of Xtampza ER when compared with nasal administration of crushed and snorted IR oxycodone.

The oral HAP study (Study 24) compared the oral abuse potential of chewed Xtampza ER relative to crushed IR oxycodone. This study found a lower abuse potential for oral Xtampza ER (either chewed or intact, fed or fasted) when compared with oral IR oxycodone.

Abuse-Deterrence Conclusions

The results from studies of Xtampza ER's abuse-deterrent properties suggests that Xtampza ER provides significant barriers against abuse and misuse, and that Xtampza ER has the potential to be more resistant to manipulation and abuse than formulations of oxycodone that are currently available.

1.3 Food and Alcohol Effects

1.3.1 Effects of Food on Xtampza ER

Pharmacokinetic Characteristics

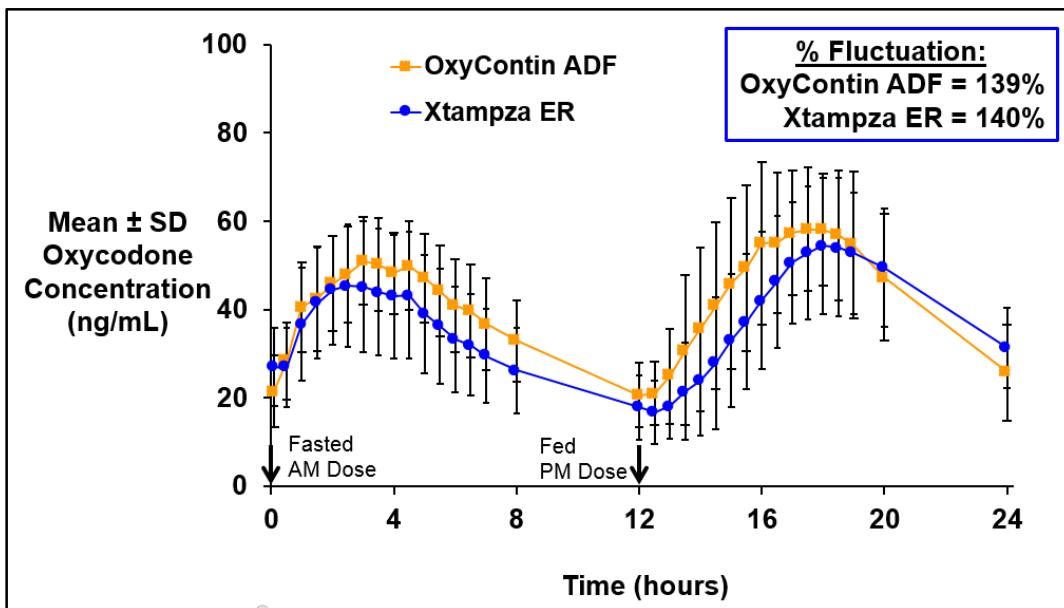
Three clinical PK studies characterized the oral bioavailability (BA) of Xtampza ER under various food conditions (i.e., fasted or fed with meals of varying size), under single-dose or steady-state conditions, and with or without naltrexone (NTX) block. NTX was used in the majority of the Phase 1 studies to block the pharmacodynamic (PD) effects of oxycodone as a safety measure in healthy subjects.

In single-dose, NTX-blocked Study 15, the PK profiles for Xtampza ER and OxyContin ADF were similar when dosed with a high-fat, high-calorie (HFHC) meal; under fasted conditions, the peak and overall exposure following Xtampza ER administration was lower than for OxyContin ADF. Study 15 also assessed the impact of the size of meals on oral BA and found that any quantity of food (i.e., low-fat, low-calorie [LFLC], medium-fat, medium-calorie [MFMC], and HFHC meals) taken with Xtampza ER produced oxycodone exposures within the range of OxyContin ADF. The proposed label for Xtampza ER therefore instructs patients to “take with food” in order to achieve an exposure equivalent to OxyContin ADF at the same dose.

Although single-dose, NTX-blocked studies are the standard for assessing the PK properties of opioid formulations in healthy subjects, these conditions are not representative of clinical use for Xtampza ER and other ER opioid products. As Xtampza ER is intended for dosing every 12 hours, steady-state conditions better represent intended clinical use and were therefore studied. Additionally, NTX co-administration is not relevant to a clinical setting of this patient population; a study conducted without NTX co-administration provided data on the magnitude of the food effect in the absence of this potential confound.

Steady-state Study 18 evaluated two scenarios of dosing for Xtampza ER and OxyContin ADF. First, a take with food “compliant” dosing condition was studied in which Xtampza ER and OxyContin ADF were dosed with food every 12 hours for 4 days, and the PK profiles were measured on Day 5. Under these conditions, the steady-state profiles for Xtampza ER were bioequivalent to OxyContin ADF. To investigate the impact of non-compliance with the take with food instruction, Study 18 also had subjects alternate a fasted/fed dosing regimen for 5 days (i.e., subjects took their AM dose fasted and their PM dose fed). On Day 5, the PK profiles were measured over both the AM and PM dosing intervals (total of 24 hours). As shown in Figure 3, the fasted morning doses were associated with a lower C_{max} and overall exposure for both Xtampza ER and OxyContin ADF when compared with the evening fed dose; the 24-hour plasma profiles were similar. Furthermore, the percent peak-trough fluctuation, which characterizes the range of plasma exposure over the 24-hour period, was nearly identical (140% and 139% for Xtampza ER and OxyContin ADF, respectively). Thus, because OxyContin ADF is regularly dosed without regard to food, this suggests that the resulting variation in plasma exposure would not be clinically relevant compared with OxyContin ADF.

Figure 3: Oxycodone Concentration under Fasted/Fed Dosing Administration at Day 5 – Study 18

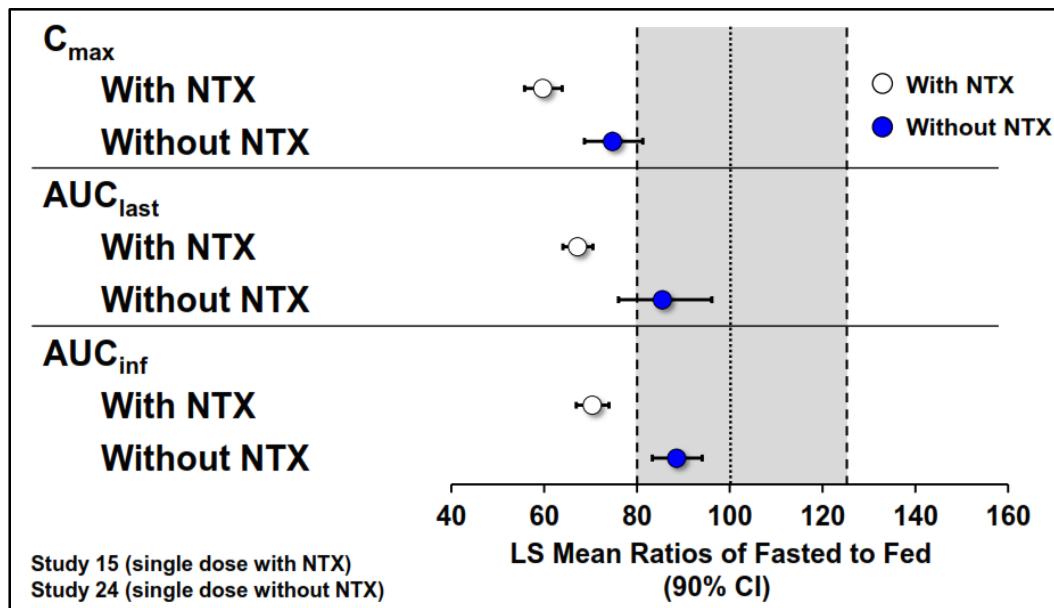


The peer-reviewed literature suggests that co-administration with NTX can increase the absorption of opioids ([Sathyam et al., 2007](#); [Bashaw et al., 1995](#)), and for oxycodone, in particular ([Purdue Pharma L.P., 2014](#)). Therefore, the effect of food on PK and PD was also assessed in Study 24, which was dosed without NTX, in part, to assess whether the food effect of Xtampza ER was impacted by NTX block.

Figure 4 illustrates the mean ratios and 90% confidence intervals (CIs) for PK parameters of interest, comparing fasted versus fed dosing. The shaded area illustrates the FDA 80%-125% BE limits; if the 90% confidence intervals fall within these bounds bioequivalence is concluded. In NTX-blocked Study 15, none of the parameters were bioequivalent when comparing fasted to fed administration of Xtampza ER. However, the effect of food on C_{max} and AUC was meaningfully reduced without NTX (Study 24), as evidenced by PK parameter ratios closer to 100%. Notably, the overall extent of absorption, AUC_{inf} , was bioequivalent when comparing fasted and fed conditions.

Taken together, these data suggest that the magnitude of the food effect is smaller under conditions that are more reflective of actual clinical use (i.e., around-the-clock dosing for patients with chronic pain without NTX), as opposed to single-dose studies with a NTX block confounder.

Figure 4: Bioequivalence Parameters for Fasted versus Fed Dosing with Xtampza ER with and without NTX Block – Studies 15 and 24



Note: Shaded area indicates bioequivalence bounds.

Clinical Food Effect Evaluation

The clinical relevance of the food effect of Xtampza ER was assessed by evaluating the clinical safety and efficacy with respect to food intake at dosing in the Phase 3 study (Study 08). The relationship between safety and the food effect with Xtampza ER was assessed using two approaches: a pre-specified independently adjudicated food effect safety analysis and a series of post-hoc meal pattern analyses. In addition to the safety assessments, an ad hoc meal pattern analysis with regard to efficacy was conducted to determine whether specific meal patterns were associated with differences in subjects' 24-hour pain score across the Phase 3 study.

In the pre-specified food effect PK safety protocol, an independent Adjudication Committee was used to determine whether serious adverse events (SAEs) and severe AEs with some level of Investigator-assessed causal relationship to study drug (termed “qualifying events”) in the Phase 3 study were related to the food consumed at the time of the qualifying event. Consistent with guidance provided by the FDA in the 2011 Type A meeting, this approach was designed to determine whether any serious safety issues might be related to the food effect. Using this approach, from over 65,000 doses of Xtampza ER taken across the Phase 3 trial, there were no SAEs or severe AEs that were found to be associated with Xtampza ER and food intake.

The second method to evaluate the potential relationship was a series of meal pattern analyses, which examined whether any specific pattern of meal sizes was associated with a higher incidence of AEs. The meals consumed on the day prior to and day of each AE were considered in the analyses. These analyses did not suggest that any association between food intake, study drug, and the incidence of AEs.

Finally, the potential impact of food consumption on efficacy was analyzed by comparing the pattern of meals consumed each day with the average daily pain score. There was also no impact of specific meal patterns on the efficacy achieved by subjects in the study.

Food Effect Conclusions

Overall, the PK data suggest an effect of food on Xtampza ER, which is diminished under conditions that more closely resemble actual clinical use conditions for patients who take ER opioids to treat chronic pain. Specifically, the effects of food on oxycodone concentration and exposure with Xtampza ER were substantially lower under both steady-state conditions (i.e., reflecting around-the-clock use) and without NTX block. The Phase 3 study, which collected data on AEs and meals taken for over 65,000 study doses of Xtampza ER, found that food intake did not have any clinical consequences on safety or efficacy. Overall, the Xtampza ER clinical development program supports a “take with food” label; the food effect with Xtampza ER is not expected to produce any clinically relevant consequences.

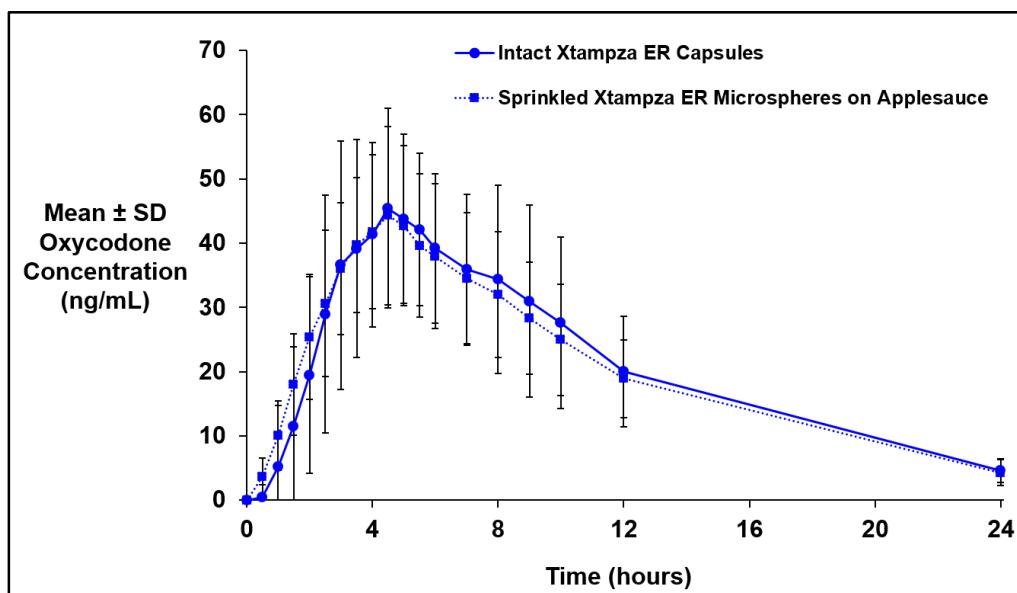
1.3.2 Effects of Alcohol on Xtampza ER

A clinical PK study (Study 26) found that co-ingestion of either 20% or 40% alcohol with Xtampza ER increased exposure relative to 0% alcohol when in the fasted state. However, peak and overall exposures following co-ingestion with either 20% or 40% alcohol were lower than for administration with 0% alcohol in the fed state. The findings show that alcohol, like food, increases exposure relative to fasted administration. However, as exposures with alcohol administration did not exceed the fed condition, there was no evidence of “dose dumping”.

1.3.3 PK of Sprinkling Xtampza ER onto Soft Foods or Directly into the Mouth

Several studies demonstrated that Xtampza ER may be administered by sprinkling the microspheres onto soft food or directly into the mouth, or may be administered via a feeding tube. A single-dose study (Study 27) demonstrated that the PK profile of Xtampza ER was BE when dosed intact orally as a capsule or when sprinkled onto applesauce in either fed (Figure 5) or fasted conditions.

Figure 5: Oxycodone Concentration following Xtampza ER Administration Intact and Sprinkled onto Applesauce under Fed Conditions – Study 27



Several in vitro studies were also conducted to assess whether the drug release characteristics and chemical stability of Xtampza ER remained consistent after mixing microspheres with other kinds of soft food. These studies demonstrated that the drug release rate and chemical stability of the formulation were not impacted by holding the microsphere/soft food mixtures at room temperature for up to an hour. Foods studied included ice cream, strawberry jam, vanilla pudding, yogurt, and applesauce.

A series of in vitro studies was also conducted to demonstrate the reliability of transfer of Xtampza ER microspheres using nasogastric (NG) tubes (10 and 12 French) and a gastrostomy tube (16 French), which were selected to cover a range of tube lengths and bore sizes used in clinical practice. Five different liquids were used to rinse the microspheres down the tubes: water, 2% milk, whole milk, and liquid nutritional supplements (Ensure and Jevity). The data demonstrate that Xtampza ER retains its ER release profile when delivered via feeding tubes using common liquid delivery vehicles used in clinical practice.

1.4 Efficacy Findings in Phase 3 Study

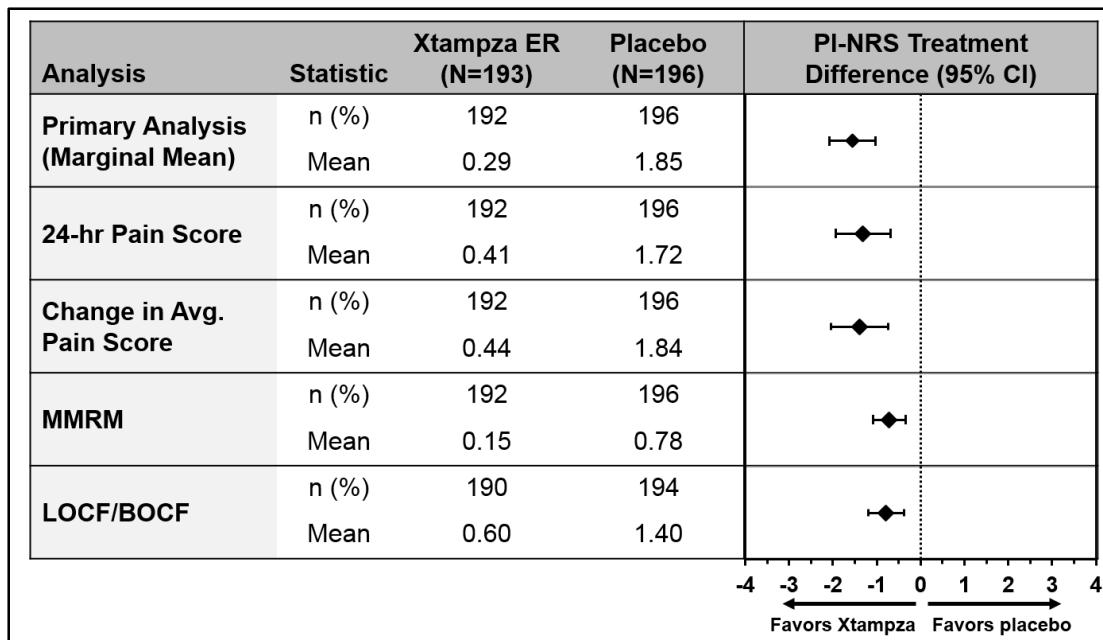
The Phase 3 study (Study 08) was an enriched-enrollment, randomized withdrawal (EERW), double-blind, placebo-controlled trial comparing the safety, tolerability, and efficacy of Xtampza ER with placebo. Enrolled subjects (both opioid-naïve and opioid-experienced) had moderate-to-severe chronic lower back pain (CLBP) for at least 6 months prior to study entry. The design conformed to FDA guidance and the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations for the design of chronic pain studies ([Dworkin et al., 2012](#)).

After a Screening Phase of up to 28 days, eligible subjects entered into an open-label Titration Phase. Doses were titrated over a period of 6 weeks to achieve a stable, optimal dose for each

subject prior to randomization in the 12-week Double-blind Maintenance Phase. The primary efficacy endpoint was change in average pain intensity score from Randomization Baseline to Week 12. In total, 740 subjects entered the Titration Phase, 389 of whom met the criteria for randomization (193 Xtampza ER, 196 placebo).

The primary efficacy endpoint of the pivotal study was met. Subjects in the Xtampza ER group had statistically significantly lower pain scores at Week 12 after randomization than subjects randomized to placebo ($P<0.0001$). The finding of significantly greater pain reductions with Xtampza ER was consistent across all sensitivity analyses (Figure 6). Details of the efficacy analysis can be found in Section 7.

Figure 6: Primary and Sensitivity Analyses of the Primary Endpoint in the Phase 3 Study



1.5 Safety Findings in the Phase 3 Study

In Phase 3 Study 08, the AEs reported were generally consistent with the AE profile of oxycodone or AEs associated with conditions typically seen in the study population. Details on the safety information from the pivotal study including the frequency of AEs, AEs leading to discontinuation, and SAEs in the Titration Phase and in the Double-blind Maintenance Phase are provided in Section 8. Xtampza ER was well-tolerated in the pivotal study; no new safety concerns were identified.

1.6 Benefit/Risk Assessment

Xtampza ER contains oxycodone in a microsphere-in-capsule formulation in which each microsphere has extended-release and tamper-resistant characteristics. Patients who have difficulty swallowing can take Xtampza ER safely by sprinkling the microspheres onto soft food

or by taking directly into the mouth because, unlike currently available ER opioid products, chewing and crushing do not increase plasma exposure relative to dosing with an intact capsule.

The development program found that the Xtampza ER formulation is more resistant than OxyContin ADF to a variety of common methods used to tamper with ER opioids for abuse using the most common routes (oral, nasal, and IV). Overall, the results of studies conducted suggest that the formulation design represents an important advancement in the development of abuse-deterrent opioids.

Product labeling will also recommend dosing with food because relative exposure is reduced when Xtampza ER is taken in a fasted state. Based upon careful analysis of the totality of the data collected from the Phase 1 and Phase 3 programs, the following conclusions have been drawn regarding the effect of food on exposure to Xtampza ER:

- Dosing Xtampza ER with any quantity of food – from a snack to a heavy meal – results in peak (C_{max}) and overall extent of exposure (AUC) within the range established by equivalent doses of OxyContin ADF when taken either fasted or fed.
- Under steady-state conditions, taking Xtampza ER in the fasted state, even at every other meal, only modestly affects drug exposure and still provides a 24-hour PK profile that is BE to OxyContin ADF dosed under the same alternating fed/fasted conditions under NTX block.
- Removing NTX as a potential confounder found that Xtampza ER had BE exposures in the fasted and fed conditions, suggesting that the magnitude of the food effect will be smaller under actual clinical-use conditions.
- In over 65,000 doses of Xtampza ER administered in the Phase 3 study, no SAEs or severe AEs related to Xtampza ER were associated with food intake. Ad hoc analyses of meal patterns showed no association of Xtampza ER and food with the incidence of AEs, or on efficacy.
- Thus, the totality of evidence supports the conclusion that under real-world conditions of dosing with food (including occasional non-compliance with the take with food instruction), Xtampza ER will provide safe and effective oxycodone exposures.

The Phase 3 study, which was based on FDA guidance and expert clinical recommendations, demonstrated that Xtampza ER has the expected safety, tolerability, and efficacy profile of an ER oxycodone product.

Overall, the Xtampza ER development program demonstrates that the microsphere formulation offers several improvements in abuse-deterrent technology over the currently marketed oxycodone products, including OxyContin ADF. This new formulation also offers patients who have difficulty swallowing access to an effective analgesic that can be crushed or chewed without increasing plasma exposure, offering significant improvements in both ease of dosing as well as patient safety.

2 UNMET MEDICAL NEED IN TREATMENT OF PAIN REQUIRING AROUND-THE-CLOCK OPIOID TREATMENT

Summary

- Chronic pain affects millions of adults in the US – more than heart disease, cancer, and diabetes combined. For select patients with chronic pain, long-term opioids can provide substantial pain relief.
- Escalating use of opioids has been shown to correlate with increasing opioid-related drug abuse.
- Common methods of intentional abuse include chewing, crushing, snorting, or otherwise manipulating an ER opioid into an IR form. Thus, one component of the public health strategy to discourage abuse has been to develop ER opioid formulations that are more difficult to manipulate or are less rewarding. FDA refers to such formulations as having “abuse-deterrent” properties.
- Most abuse-deterrent ER formulations that have been introduced into the market are hard tablets that resist crushing. While there has been a reduction in tampering with these products, they can still be abused by chewing, crushing, injecting, and snorting.
- Hard tablet formulations can also create a serious treatment challenge for the estimated 11 million US patients with chronic pain who cannot swallow pills or who have difficulties swallowing.
- Despite warnings in the labels, healthcare providers and their patients with chronic pain and difficulty swallowing often unintentionally misuse ER opioid analgesics by crushing tablets or opening capsules to aid in dose administration.
- There is an unmet need for an improved abuse-deterrent opioid formulation that can also accommodate patients who have difficulty swallowing.

2.1 Background on Chronic Pain

Chronic pain affects millions of Americans, with a prevalence higher than heart disease, cancer, and diabetes combined ([American Academy of Pain Medicine, 2013](#)). Chronic pain arises from diverse etiologies including lower back pain, osteoarthritis, and cancer ([Argoff and Kopecky, 2014](#)). Lower back pain is the fifth most frequent reason for office visits in the US ([Lange et al., 2010](#)).

Chronic pain is often treated with opioid medications. Opioid medications can provide short-, intermediate-, or long-acting analgesia depending upon the specific properties of the medication and whether or not it is formulated as an ER drug. ER/long-acting (LA) opioids are typically used for around-the-clock, maintenance treatment, and short-acting IR opioids are typically co-prescribed with an ER opioid to treat breakthrough pain.

Currently approved ER/LA mu-agonist opioids are: methadone, hydrocodone, fentanyl, morphine, buprenorphine, hydromorphone, oxycodone, oxymorphone, and tapentadol. These currently approved oral ER/LA opioids have limitations, including continued concern about abuse and misuse in the intended patient population.

2.2 Abuse of Extended-Release Opioid Products

The Centers for Disease Control and Prevention (CDC) estimates that, from 1999 to 2012, the number of opioid overdose deaths increased four-fold, from approximately 4,000 to 16,000 deaths per year ([Warner et al., 2014](#)). Approximately 1.9 million people in the US are dependent on or abuse pain relievers ([Substance Abuse and Mental Health Services Administration, 2014](#)).

Opioid medications are often manipulated for purposes of abuse. A common method for opioid abuse is transforming ER opioids into an IR form for oral, IN, or IV administration. In an effort to combat such forms of abuse, opioid formulations have been developed which include the addition of an antagonist or dosage forms with physical and chemical characteristics to decrease effectiveness of tampering. However, even with formulation advancements, people continue to abuse ER opioids by crushing and chewing, injecting, and insufflating (also known as snorting).

In 2010, Purdue Pharma, L.P. introduced reformulated OxyContin controlled-release (OxyContin ADF), a hard tablet with gelling properties on exposure to water. The introduction of OxyContin ADF decreased abuse compared with the original formulation, but available data demonstrate that relatively simple manipulations such as simply chewing the tablets or crushing with common household tools defeat the controlled-release mechanism, in effect, creating an IR oxycodone. OxyContin ADF, therefore, retains warnings that “crushing, chewing, or dissolving OXYCONTIN tablets can cause rapid release and absorption of a potentially fatal dose of oxycodone” ([Purdue Pharma L.P., 2014](#)).

An analysis recently commissioned by Collegium examined the prevalence of manipulation before oral administration for OxyContin ADF and two other available products (Opana ER and Nucynta ER) designed as hard-to-crush tablets that use a similar delivery technology. The analysis examined the prevalence of various administration routes used in the last 30 days among abusers entering substance abuse treatment. Approximately 40% of oral abusers of these formulations reported manipulating them before swallowing; chewing was the most prevalent manipulation method (approximately 35%) ([Butler and Black, manuscript in preparation](#)). These data highlight the need for continued advances in abuse-deterrent formulation technology for ER opioids.

2.3 Unmet Medical Need in Patients Requiring Opioid Treatment Who Have Difficulty Swallowing

An unintended consequence of the reformulation of OxyContin ADF and other ER opioids as hard tablets is increased difficulty swallowing for many patients. It is estimated that over 11 million patients in the US with chronic pain either have difficulty swallowing pills or dislike swallowing pills ([Pergolizzi et al., 2014](#)). FDA has estimated that as many as 40% of Americans may suffer from difficulty swallowing, a problem which it has called out in its guidance on the

size and shape of generic dosage forms ([CDER, 2015c](#)). Children and elderly patients, in particular, are more likely to have difficulty swallowing tablets or capsules ([CDER, 2015c](#)). Patients with severe dysphagia may even require analgesic administration through an enteral tube.

The need for dosing flexibility is a particular concern for oxycodone because OxyContin ADF, must not be crushed or chewed to facilitate swallowing or be administered via a feeding tube. The OxyContin ADF label carries warning statements such as “Instruct patients to swallow OxyContin tablets intact. Crushing, dissolving, or chewing the tablet can cause rapid release and absorption of a potentially fatal dose of oxycodone.” Notably, OxyContin ADF, and other hard tablet formulations have also been associated with post-marketing reports of choking, gagging, regurgitation, and tablets stuck in the throat. Accordingly, the OxyContin ADF label also instructs “consider use of an alternative analgesic in patients who have difficulty swallowing.”

Despite warnings, there are reports of healthcare providers and their patients who have chronic pain manipulating ER opioid analgesics by crushing or chewing tablets, respectively, or opening ER capsules to aid with dose administration; this practice can lead to medication errors such as under- or over-dosing, change in the release profile of the analgesic leading to adverse effects, and alteration of analgesic efficacy. A relatively recent study conducted at teaching hospitals found that medication errors are more common among those with dysphagia (21%) than those without (6%) ([Kelly et al., 2011](#)). To elaborate, altering an ER formulation changes the PK characteristics (increased C_{max} and possibly AUC), constitutes misuse depending upon the context, and can lead to improper dosing and even overdosing resulting in death. Additionally, some abuse-deterring formulations release an antagonist when crushed, which can lead to exacerbation of pain and/or withdrawal symptoms.

Patients with chronic pain who cannot swallow solid, oral dosage forms have limited treatment options – including transdermal patches, IR opioids, methadone, and certain ER opioids – which creates a treatment challenge that can lead to inadequate pain management. Transdermal patches may have unreliable absorption. Immediate-release formulations also have limitations in that they have to be administered every four to six hours including throughout the night to maintain pain control. Methadone has high PK variability, many drug-drug interactions, and may lead to QTc interval prolongation and serious arrhythmia. Some of the limitations of available opioid formulations are described in Table 1.

Table 1: Limitations of Currently Marketed Opioid Formulations

Fentanyl Patch	IR Opioid	Methadone	ER Opioids
<ul style="list-style-type: none">• May have unreliable absorption, particularly in geriatrics• Dermal side effects including skin rash and erythema	<ul style="list-style-type: none">• May need to be administered up to 4 to 6 times per day, which can adversely affect patient compliance due to the significant pill burden	<ul style="list-style-type: none">• Potential for QTc interval prolongation and serious arrhythmia during treatment• Significant drug interaction potential	<ul style="list-style-type: none">• Labeled to not be crushed, dissolved, or chewed because rapid release of drug can result in fatal overdose• Difficulty swallowing reported for hard tablets

To address this unmet medical need in patients who have chronic pain with dysphagia, a dosage form is needed that affords flexible dosing options such as administration by sprinkling onto soft foods without the worry of bolus dosing and subsequent exacerbation of potentially serious adverse effects if a patient inadvertently chews the formulation, or the ability to administer the formulation through enteral tubes without the concern for tube blockage or drug interaction with common administration media such as water or tube feeds (e.g., Ensure). Xtampza ER was designed to address the needs of this patient population.

3 OVERVIEW OF XTAMPZA ER FORMULATION AND DEVELOPMENT PROGRAM

Summary

- Xtampza ER is a novel, abuse-deterrent, ER microsphere-in-capsule opioid formulation. The microsphere design allows for flexible dosing options such as administration onto soft foods or delivery via feeding tube.
- The 505(b)2 application was supported by clinical PK studies as well as one placebo-controlled safety and efficacy study and an extensive evaluation of the abuse deterrent characteristics of the product.
 - Xtampza ER was subjected to a comprehensive evaluation of abuse-deterrent properties consistent with FDA's guidance; studies included in vitro manipulation and extraction (Category 1), PK of manipulated product (Category 2) and human abuse potential (Category 3).
 - The relative bioavailability of Xtampza ER compared with OxyContin ADF was characterized under single-dose and steady-state conditions.
 - The clinical PK program extensively characterized oxycodone plasma exposure following administration of Xtampza ER under various food or alcohol conditions.
 - Alternative dosing studies (in vitro and clinical PK studies) were conducted to demonstrate that Xtampza ER provides flexible dosing options (e.g., sprinkle dosing, feeding tube administration).
 - The safety, tolerability, and efficacy of Xtampza ER was demonstrated in a double-blind, placebo-controlled, enriched enrollment, randomized withdrawal clinical trial in opioid-experienced and opioid-naïve patients with moderate-to-severe chronic low back pain.

3.1 Product Characteristics

The Xtampza ER formulation consists of microspheres that are filled into a capsule. Each microsphere, whether inside or outside the capsule, is designed to be abuse-deterrent and extended-release; this design lends itself to flexible dosing options such as sprinkling onto foods or delivery via feeding tube. The active ingredient is homogenously dispersed in each microsphere.

Xtampza ER microspheres have a median particle size of approximately 300 microns and are comprised of the active ingredient (oxycodone), a fatty acid, waxes and a surfactant. The inactive ingredients in Xtampza ER microspheres have a history of use in food and oral pharmaceuticals. The microspheres are formulated through a melt process in which the active ingredient, as a free base, is combined with fatty acid, wax, and surfactant excipients to form a molten solution in

which the base is solubilized via an ionic interaction with the fatty acid. The resulting homogenous liquid is sprayed into small droplets using a proprietary atomization process. The droplets rapidly congeal into solid microspheres. Differing product strengths are achieved by varying the weight of the microspheres loaded into a capsule. Five product strengths have been developed (Table 2). Because Xtampza ER is not formulated using oxycodone HCl, but instead uses the base form of oxycodone, FDA guidance mandates that the commercial product strengths reflect the amount of oxycodone contained in the capsule, rather than the HCl salt ([CDER, 2015b](#)); throughout this briefing book the strengths will be referred to in terms of the equivalent dose of oxycodone HCl in order to facilitate comparison with marketed reference products.

The Xtampza ER formulation is designed to be administered every 12 hours. Due to the composition and hydrophobic nature of Xtampza ER microspheres, drug release is suppressed when the formulation is dosed under fasted conditions relative to fed conditions (Section 5.2).

Table 2: Xtampza ER Dosage Strengths

Xtampza ER Strengths, Oxycodone (mg)	Equivalent Amount of Oxycodone HCl (mg)
9	10
13.5	15
18	20
27	30
36	40

3.2 Key FDA Milestones and Guidance During Development

Xtampza ER was granted Fast Track designation in December 2007 and developed as a 505(b)(2) with OxyContin ADF as the reference product. The NDA contains bioavailability data comparing Xtampza ER to OxyContin ADF, and full reports of investigations of safety and effectiveness sponsored by Collegium. The NDA was accepted for filing by the FDA in February 2015 and the PDUFA date is 12 Oct 2015.

FDA provided input through meetings and advice letters on the studies necessary to evaluate abuse-deterrence, and the studies conducted on Xtampza ER are consistent with FDA final guidance on the evaluation and labeling of abuse-deterrent opioids ([CDER, 2015a](#)).

A Type A Meeting was held in August 2011 where FDA provided specific guidance on the Phase 3 study design including characterization of the product's food effect. FDA requested an evaluation of food consumption and its effect on safety and efficacy. In response to FDA's recommendation, the Phase 3 trial incorporated a pre-specified safety protocol to evaluate the impact of food consumption and Xtampza ER on exacerbation of SAEs/severe AEs. In addition, Collegium completed single-dose and steady-state PK studies to characterize the plasma profile of the product under varying conditions of food intake.

3.3 Overview of Abuse-Deterrence Evaluation

Xtampza ER was developed and evaluated in a manner consistent with recommendations described in FDA's guidance on the evaluation and labeling of abuse-deterrent opioids ([CDEER, 2015a](#)) and with specific feedback from FDA throughout the development program. Collegium's comprehensive development program consisted of in vitro (laboratory-based) and clinical studies, the results of which indicate that Xtampza ER may be more resistant to abuse by manipulation followed by oral ingestion, snorting or attempted IV injection than OxyContin ADF.

3.3.1 Category 1 Studies – In Vitro Manipulation and Extraction Studies

Collegium conducted a series of Category 1 studies to investigate the ease with which Xtampza ER might be tampered with to potentially accelerate drug release after oral or nasal administration, or to possibly enable IV injection or abuse by smoking. These in vitro laboratory studies were also designed to compare the abuse-deterrent properties of Xtampza ER with that of OxyContin ADF and IR oxycodone. The study designs were based on recommendations set forth by the FDA to evaluate "real-world" tampering scenarios, encompassed the types of assessments conducted by other sponsors for products with abuse deterrent attributes including OxyContin ADF, and investigated the common methods of abuse used by abusers as described in the literature as well as on internet web sites.

3.3.2 Category 2 Studies – Pharmacokinetics

Collegium conducted five Category 2 studies designed specifically to examine the effects of product manipulation on the PK of Xtampza ER (Table 3).

Table 3: Overview of Category 2 Studies

Study	Subjects ^a	Conditions	Comparator(s)	Key Objective
17 (Oral)	42	<ul style="list-style-type: none">• Single dose• NTX block• Fed and fasted	<ul style="list-style-type: none">• IR oxycodone solution	<ul style="list-style-type: none">• Assess the safety and PK of Xtampza ER intact, chewed and crushed
25 (Oral)	40	<ul style="list-style-type: none">• Single dose• NTX block• Fed	<ul style="list-style-type: none">• OxyContin ADF (intact and crushed)• Crushed IR tablets	<ul style="list-style-type: none">• Assess the safety and PK of Xtampza ER, intact and crushed; compare with intact and crushed OxyContin ADF
19 (Nasal)	13	<ul style="list-style-type: none">• Single dose• NTX block• Fed	<ul style="list-style-type: none">• Oxycodone powder	<ul style="list-style-type: none">• Assess the safety and PK of crushed Xtampza ER following nasal administration; compare with intact oral administration

Study	Subjects ^a	Conditions	Comparator(s)	Key Objective
21 (Nasal) ^b	36	<ul style="list-style-type: none"> • Single dose • No NTX block • Fed 	<ul style="list-style-type: none"> • Crushed IR oxycodone tablets 	<ul style="list-style-type: none"> • Assess the safety and PK of crushed Xtampza ER following nasal administration; compare with intact oral administration
24 (Oral) ^b	47	<ul style="list-style-type: none"> • Single dose • No NTX block • Fed and fasted 	<ul style="list-style-type: none"> • Crushed IR oxycodone tablets in solution 	<ul style="list-style-type: none"> • Assess the safety and PK of Xtampza ER, intact and chewed

NTX = naltrexone. ^a Indicates number of subjects in the PK population; ^b Subjective endpoints were also assessed in these clinical HAP studies (See Section 3.3.3)

3.3.3 Category 3 Studies – Human Abuse Potential

Collegium conducted two Category 3 studies designed to assess the HAP for oral and IN abuse with Xtampza ER in 2 clinical studies, which also collected PK data (Table 4).

Table 4: Overview of Category 3 Studies

Study	Subjects ^a	Conditions	Comparator(s)	Key Objective
21 (Nasal)	36	<ul style="list-style-type: none"> • Single dose • No NTX block • Fed 	<ul style="list-style-type: none"> • Crushed IR oxycodone tablets 	<ul style="list-style-type: none"> • Evaluate the human abuse potential of crushed Xtampza ER via the nasal route of abuse
24 (Oral)	47	<ul style="list-style-type: none"> • Single dose • No NTX block • Fed and fasted 	<ul style="list-style-type: none"> • Crushed IR oxycodone tablets in solution 	<ul style="list-style-type: none"> • Evaluate the human abuse potential of intact and chewed Xtampza ER via the oral route of abuse

NTX = naltrexone. ^a Indicates number of subjects in the PK population.

3.4 Relative Bioavailability and Food- and Alcohol-Effect Studies

Collegium conducted four clinical PK studies that characterized the oral BA of Xtampza ER under various food or alcohol conditions (e.g., fasted or fed with meals of varying size, sprinkled on applesauce) and under single-dose or steady state conditions (Table 5).

Table 5: Overview of Food- and Alcohol-Effect Studies

Study	Subjects ^a	Conditions	Comparator(s)	Key Objective
15 (Oral)	48	<ul style="list-style-type: none"> • Single dose • NTX block • Fed and fasted 	• OxyContin ADF	<ul style="list-style-type: none"> • Assess the safety and PK of Xstampza ER in fed (at low-, medium-, and high-fat/calorie levels) and fasted states and the relative BA to OxyContin ADF
18 (Oral)	39	<ul style="list-style-type: none"> • Steady state • NTX block • Fed and fasted 	• OxyContin ADF	<ul style="list-style-type: none"> • Assess the safety and PK of Xstampza ER in high-fat/calorie meal for all doses, or fasted morning dose and high-fat/calorie meal with evening dose compared to OxyContin ADF under the same conditions
24 (Oral)^b	47	<ul style="list-style-type: none"> • Single dose • Fed and fasted 	• N/A	<ul style="list-style-type: none"> • Assess the safety and PK of Xstampza ER in high-fat/calorie meal and fasted states without NTX block
26 (Oral)	43	<ul style="list-style-type: none"> • Single dose • NTX block • Fed and fasted 	<ul style="list-style-type: none"> • Xstampza ER fasted with alcohol (0-40%) and fed without alcohol 	<ul style="list-style-type: none"> • Assess the safety and PK of Xstampza ER (40 mg) co-ingested with 0%, 20%, 40% alcohol in the fasted state

NTX = naltrexone. ^a Indicates number of subjects in the PK population; ^b Subjective endpoints were also assessed in this clinical HAP study (See Section 3.3.3)

3.5 Dosage and Administration Studies

Several in vitro studies and one in vivo PK study assessed the flexibility of dosing with Xstampza ER (Table 6).

Table 6: Overview of Clinical Dosage and Administration Study

Study	Subjects ^a	Conditions	Comparator(s)	Key Objective
27 (Oral)	43	<ul style="list-style-type: none"> • Single dose • NTX block • Fed and fasted 	<ul style="list-style-type: none"> • Xstampza intact (fed and fasted) and Xstampza ER sprinkled 	<ul style="list-style-type: none"> • Assess the safety and PK of intact Xstampza ER and Xstampza ER sprinkled on applesauce

NTX = naltrexone. ^a Indicates number of subjects in the PK population

3.6 Phase 3 Safety, Tolerability and Efficacy Clinical Study

Collegium's Phase 3 clinical study (Study 08) was a double-blind, placebo-controlled, enriched enrollment, randomized (n=389) withdrawal study. Safety, tolerability, and efficacy of Xstampza

ER was compared with placebo in subjects with moderate-to-severe CLBP who required around-the-clock opioid treatment.

In the Phase 3 study, a food-effect PK safety protocol was implemented to collect detailed information on occurrence of AEs and food consumption. The safety protocol included assessment by an independent, expert committee that adjudicated the relationship between food consumption, Xtampza ER, and AE occurrence. Additionally, an electronic diary was used to collect data on the timing of dosing and food consumption. Data were also collected on meal size (no meal, snack, light meal, or heavy meal). A post hoc analysis evaluated potential associations between food intake at dosing and safety (i.e., AEs) and efficacy (i.e., mean daily pain scores).

4 ABUSE DETERRENT EVALUATION

Summary

- Collegium conducted a comprehensive evaluation of the abuse-deterrent properties of Xtampza ER, which is consistent with FDA's Final Guidance, "*Abuse Deterrent Opioids – Evaluation and Labeling*"(2015)
- Category 1 (Laboratory Manipulation and Extraction)
 - Physical manipulation studies demonstrated that Xtampza ER was more resistant to crushing than OxyContin ADF.
 - Xtampza ER provided greater resistance to manipulation and extraction in commonly available, ingestible solvents relative to OxyContin ADF and IR oxycodone.
 - Xtampza ER provided resistance to manipulations to prepare the microspheres for IV injection.
 - Smoking is not anticipated to be a preferred route of abuse for Xtampza ER based on results of vaporization studies which simulate smoking.
- Category 2 (Pharmacokinetics [PK])
 - Xtampza ER microspheres maintained an extended-release profile when administered crushed or chewed; these manipulations did not increase peak plasma exposure relative to intact capsules
 - Crushed Xtampza ER microspheres were bioequivalent to intact capsules whereas crushed OxyContin ADF had a plasma profile bioequivalent to IR oxycodone.
 - Crushed and snorted Xtampza microspheres demonstrated a lower C_{max} and similar T_{max} when compared with intact oral administration of the capsules.
- Category 3 (Human Abuse Potential [HAP])
 - A nasal HAP study demonstrated that crushed and snorted Xtampza ER microspheres had lower drug liking than snorted IR oxycodone. Drug liking of crushed and snorted Xtampza ER was also lower than for intact oral administration.
 - An oral HAP study conducted on chewed and intact Xtampza ER microspheres demonstrated that Xtampza ER (chewed and intact) had lower drug liking than crushed IR oxycodone under both fed and fasted conditions.
- Overall, data from laboratory studies, PK studies, and HAP studies, including comparative studies to OxyContin ADF and IR oxycodone, demonstrated the abuse-deterrent properties of Xtampza ER. Based on these studies, it is anticipated that Xtampza ER has the potential to be more resistant to manipulation and abuse than currently available formulations of oxycodone.

4.1 Category 1: In Vitro Manipulation and Extraction

Category 1 studies were in vitro laboratory manipulation and extraction studies to evaluate the ease with which the abuse-deterrent properties of the Xtampza ER formulation can be defeated or compromised (Table 7). As the capsules are produced by varying the fill weight of microspheres, the composition of the various strengths is identical. Therefore, Category 1 studies were conducted using the highest strength of Xtampza ER (40 mg). Comparators tested included OxyContin ADF (40 mg) and IR oxycodone (30 mg).

Table 7: Category 1 Abuse-Deterrent Studies

		Experiment	Objective
General Manipulation	Physical	Particle Size Reduction (PSR) studies	Investigate effect of household tools on increasing drug release (key conclusions verified by independent third party laboratory)
	Chemical	Extraction studies	Assess drug release rate into multiple solvents under different conditions
Route Specific	IV Injection	Small volume extraction for IV injection	Evaluate extraction of drug into injectable amounts of water
		Direct injection	Assess ability to suspend in water or melt for direct injection
	Smoking	Simulated smoking abuse study	Quantify drug vaporized on application of heat

4.1.1 Particle Size Reduction Studies

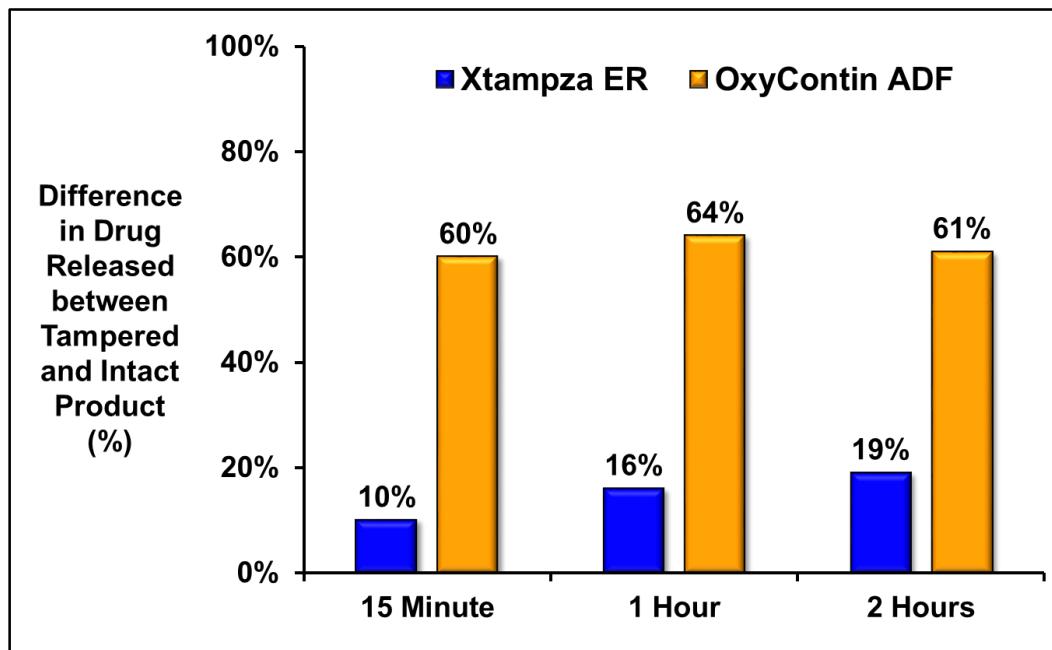
In total, 11 common household tools were evaluated for their ability to produce reductions in particle size of Xtampza ER and OxyContin ADF, which was used as a comparator. The most effective tool for particle size reduction (PSR) for Xtampza ER microspheres (Tool A) produced a reduction in the median particle size of approximately 20%. The next most effective PSR tool (Tool B) produced a reduction in the median particle size of approximately 15%, and the remaining nine tools produced a <10% reduction in microsphere particle size. In contrast, eight of the 11 tools produced significant deformation or particle size reduction when applied to OxyContin ADF tablets. Particle size reduction of these comparator tablets was visually apparent due to the large starting size of the tablet.

The rate of drug release was measured using in vitro dissolution at several time points over 12 hours for tools that were effective in reducing particle size of Xtampza ER microspheres. In vitro dissolution provides an estimate of how drug will be released in the body when ingested. For Xtampza ER, none of the PSR manipulations produced increases in percent drug release of 20% or more compared to intact control at any time point over 12 hours, indicating manipulated product retained extended-release characteristics. In contrast, 7 tools increased the percent of drug released by ≥20% compared with the intact control as soon as 15 minutes. At least 4 of the

techniques resulted in a significant acceleration of release ($\geq 50\%$ increase in dissolution) within 15 minutes that could be classified as “dose dumping”, defined as the unintended, rapid drug release in a short period of time of the entire amount or a significant fraction of the drug contained in a modified-release dosage form (Meyer and Hussain, 2005). Similarly, none of the tools were able to double the amount of drug released for Xtampza ER by 15 minutes, whereas seven of the 11 tools were able to double the drug released for OxyContin ADF.

Figure 7 displays the difference in the percent drug released comparing tampered and intact product at the 15 minute time point of dissolution using the most effective tool identified for each respective product in the study (Tool A for Xtampza and Tool G for OxyContin ADF).

Figure 7: Impact of Most Effective Manipulation Tools on Drug Release for Xtampza ER and OxyContin ADF



The key findings from the physical manipulation studies were verified by testing in a third party, independent laboratory. Taken together, the results from the physical manipulation studies showed that the unique physicochemical properties of Xtampza ER provide robust resistance to multiple forms of physical manipulation compared with OxyContin ADF.

4.1.2 Optimization Study for Method A

The optimization study evaluated various conditions under which the effectiveness of the best PSR tool for Xtampza ER, Tool A, could be maximized. Conditions evaluated include the number of capsules manipulated, the duration of manipulation, and the construction of the tool. The most effective combination of these conditions for Tool A was used to crush Xtampza ER for all subsequent in vitro extraction studies, in vivo PK studies, and human abuse potential studies that required a crushed manipulation.

4.1.3 Heat and Freeze PSR Study

This study evaluated whether pre-treating Xtampza ER microspheres by heating or freezing increased the effectiveness of crushing using the 3 most effective PSR tools. The effect of PSR was measured by quantifying drug release over time using an in vitro dissolution procedure. Findings from the study showed that pre-freezing with physical manipulation did not increase the effectiveness of crushing Xtampza ER microspheres compared with manipulations applied without pre-freezing.

Pretreatment with heating fused the Xtampza ER microspheres into a solid mass, such that subsequent attempts to reduce particle size with physical manipulation yielded larger particle size and slower drug release rates than that of the intact, unmanipulated microspheres.

4.1.4 Chemical Manipulation

Extraction studies were conducted to evaluate the rate of drug release in common, ingestible solvents with a range of polarity and pH. The dosage forms were crushed using the most effective respective methods for each product established in the PSR studies.

At room temperature under continuous agitation, drug extraction from both intact Xtampza ER microspheres and intact OxyContin ADF tablets was low over the first two hours (<30% extracted) and was incomplete at 8 hours in all solvents (<70% released). IR oxycodone was extracted more rapidly (>60% within 15 minutes in all but one solvent) as would be expected for an IR formulation.

When the products were crushed before solvent extraction, the amount of drug extracted from OxyContin ADF and IR Oxycodone was significantly higher than Xtampza ER at the early time points in 6 of the 7 ingestible household solvents (Table 8). The exception was Solvent G, which was not effective in increasing extraction for any of the manipulated formulations.

Table 8: Average Percent of Drug Extracted from Crushed Xtampza ER vs Crushed OxyContin ADF and IR Oxycodone at Room Temperature with Continuous Agitation

Time	Solvent	Mean (SD) % of Drug Extracted		
		Xtampza ER	OxyContin ADF	IR Oxycodone
15 minutes	A	2% (0.4)	77% (1.6)	93% (3.7)
	B	5% (0.9)	82% (3.8)	90% (1.3)
	C	6% (2.3)	82% (1.2)	95% (1.2)
	D	8% (1.9)	44% (1.2)	95% (2.0)
	E	9% (1.3)	76% (3.8)	82% (2.1)
	F	2% (0.2)	82% (4.1)	97% (0.7)
	G	2% (0.7)	<1% (0.1)	1% (0.02)
1 hour	A	4% (1.3)	85% (3.7)	94% (4.1)
	B	10% (2.2)	90% (3.8)	92% (1.7)
	C	11% (3.6)	90% (1.8)	95% (2.1)
	D	17% (4.0)	43% (0.8)	97% (1.4)
	E	19% (5.4)	84% (4.4)	86% (3.1)
	F	4% (0.4)	89% (3.5)	97% (1.0)
	G	2% (0.6)	<1% (0.1)	1% (0.2)
8 hours	A	10% (0.7)	89% (3.2)	*
	B	22% (3.7)	96% (3.3)	*
	C	34% (6.0)	91% (0.7)	*
	D	39% (4.4)	40% (0.3)	*
	E	77% (10.5)	95% (3.0)	*
	F	8% (0.7)	96% (1.6)	*
	G	5% (0.9)	1% (0.1)	1% (0.2)

Note: * IR oxycodone not tested at 8 hours for most solvents because extraction was complete at earlier time points.

When crushed products were tested at elevated temperatures, the extraction of drug from Xtampza ER was increased in several solvents relative to the room temperature. However, the quantity of drug extracted at 15 minutes was lower from Xtampza ER when compared with both IR oxycodone and OxyContin ADF in all ingestible household solvents except Solvent G, which was an ineffective solvent for all products.

To investigate procedures that sophisticated drug users with some chemistry knowledge and laboratory equipment might employ, a series of extraction studies were performed with advanced

solvents. The studies included secondary extraction steps to understand the efficiency of further drug extraction into an injectable and ingestible solvent. Seven advanced solvents were tested that included protic and aprotic organic solvents, as well as strongly acidic and basic solvents.

More than 50% of the drug could be extracted for 5 advanced solvents for crushed Xtampza ER, OxyContin ADF, and IR oxycodone in the primary extraction. However, the amount of drug that could be extracted from Xtampza ER in a secondary extraction step which could be used for injection or ingested was <5% for all solvents, whereas significant recovery was achieved for 5 of the advanced solvents for OxyContin ADF and IR oxycodone (Table 9).

Table 9: Average Percent of Drug Extracted Following Secondary Extraction for Crushed Xtampza ER, OxyContin ADF, and IR oxycodone

Solvent	Mean (SD) % of Drug Extracted in Secondary Extraction		
	Xtampza ER	OxyContin ADF	IR Oxycodone
H	4% (0.1)	76% (2.2)	56% (8.5)
I	5% (0.6)	48% (3.4)	48% (1.2)
J	1% (0.1)	5% (0.4)	0.3% (0.3)
K	4% (0.2)	37% (3.8)	59% (0.4)
L	4% (0.5)	84% (0.5)	66% (1.9)
M	3% (0.5)	74% (0.9)	49% (2.0)

4.1.5 Route Specific Method of Abuse: IV Injection

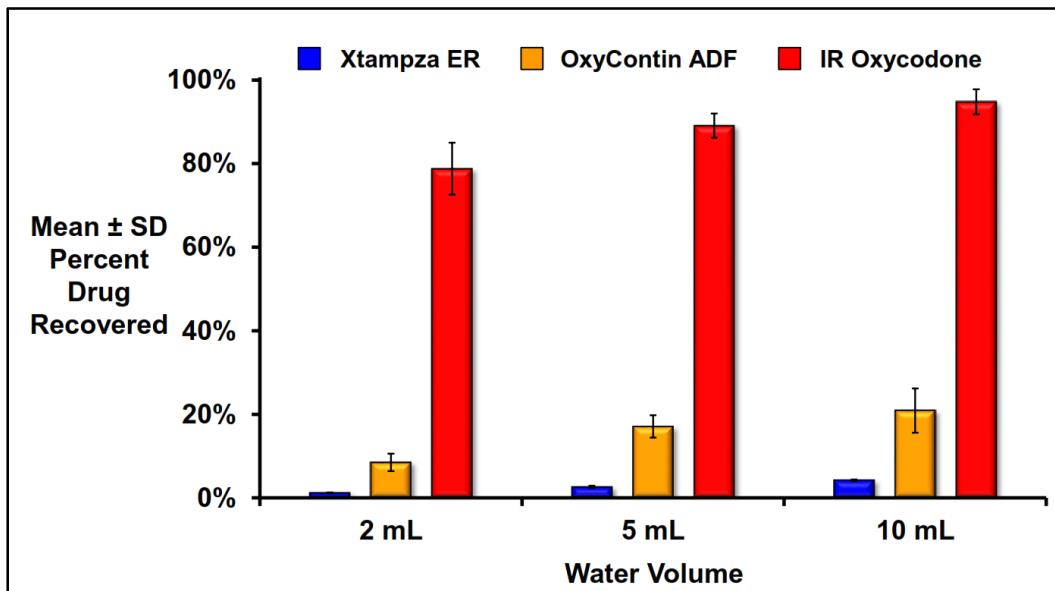
Several studies were conducted to evaluate the potential for IV abuse of Xtampza ER.

Room Temperature Extraction in Small Volumes of Water

When crushed and extracted in small volumes of water (2 mL, 5 mL, and 10 mL) at room temperature, less than 1% of oxycodone contained in Xtampza ER capsules was recovered in the filtrate. Extraction for both OxyContin ADF and IR oxycodone was a function of the volume tested, with the 10 mL volume being most effective in extracting oxycodone (average recoveries of 10% and 89%, respectively).

Boiling Point Extraction in Small Volumes of Water

The small volume extraction study was also conducted on crushed products in water at its boiling point. In this condition, <5% of oxycodone was recovered in the filtrate from Xtampza ER for all volumes of water tested, compared to 9-21% for OxyContin ADF and 80% or more for IR oxycodone (Figure 8).

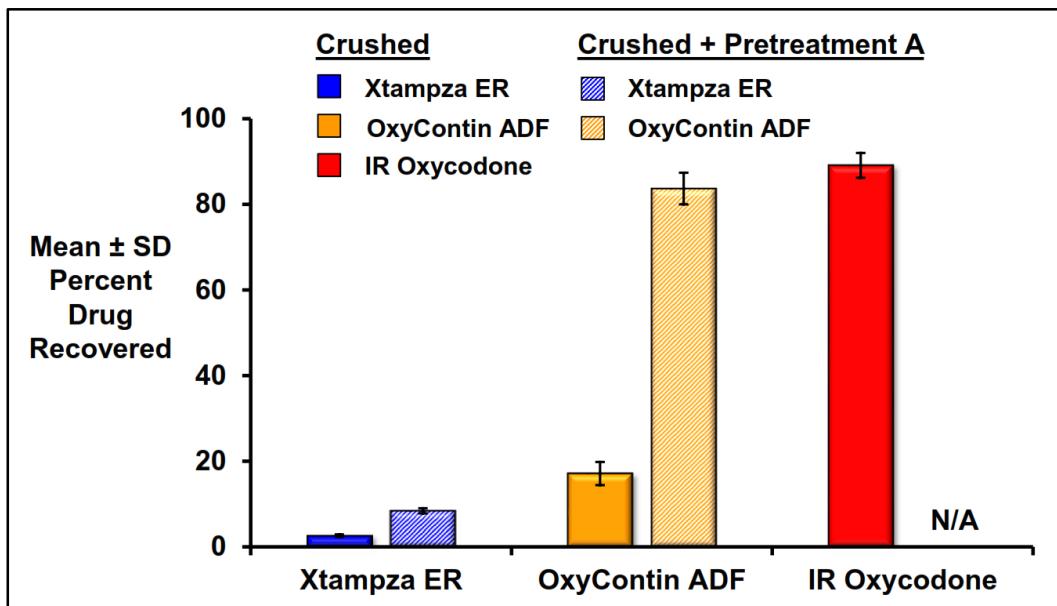
Figure 8: Extraction Following Crushing and Exposure to Water at Boiling Point

Extraction in Small Volumes of Water- Extended Exposure Times

To test an extreme case, small volume extractions in water were conducted for extended exposure times of 30 minutes at room temperature and near the point of boiling. At room temperature, the percent of drug recovered from Xtampza ER remained low (<3% across conditions). For the heated samples the percent drug recovered was 6% and 11% for the 5mL and 10mL volumes, respectively. Under the same conditions the maximum amount recovered from OxyContin ADF ranged from 22% to 50%.

Boiling Point Extraction in Small Volumes of Water with Pretreatment A

This study was conducted by applying a pretreatment procedure (Pretreatment A) to the crushed dosage forms prior to extraction. This pretreatment procedure is described on the internet as a means to prepare OxyContin ADF for IV injection. The amount of oxycodone released from OxyContin ADF increased from a mean of 17% without pretreatment to a mean of 84% with pretreatment. However, the pretreatment showed little impact on extraction of oxycodone from Xtampza ER (Figure 9).

Figure 9: Extraction Following Crushing, Pretreatment A, and Exposure to Water at Boiling Point

Injectability of Suspension of Xtampza ER in Water

Xtampza ER microspheres were suspended in water and an attempt was made to force the microsphere/water suspension through various gauge needles (27 gauge, 22 gauge, and 18 gauge). The 18 gauge needle reflects an extreme case because it is not commonly used by abusers due to the large size of the needle and the potential to cause vein damage.

Results of the study indicate that Xtampza ER microspheres suspended in water did not effectively pass through various sized needles, regardless of whether the microspheres were crushed before suspending. Microspheres were not able to be expelled through 27 or 22 gauge needles regardless of the volume tested. With an 18 gauge needle, the average mass of solid microspheres passed was a fraction of the total solid capsule fill for the largest volume tested: 1.3% for intact microspheres, and 13.6% for crushed microspheres.

Syringability of Melt of Xtampza ER

After melting Xtampza ER microspheres, it was impossible to draw any molten material into a syringe using needle diameters smaller than 18 gauge. Even when using the largest needle size (18 gauge), the molten material solidified inside the syringe and was impossible to expel.

4.1.6 Route Specific Method of Abuse: Smoking

Data collected characterizing rates of abuse and routes of administration have consistently reported a relatively low incidence of smoking for oxycodone containing products compared to the more prevalent routes of oral, nasal and IV administration. This is true for immediate release formulations as well as both the original and reformulated OxyContin formulation (6.4% and

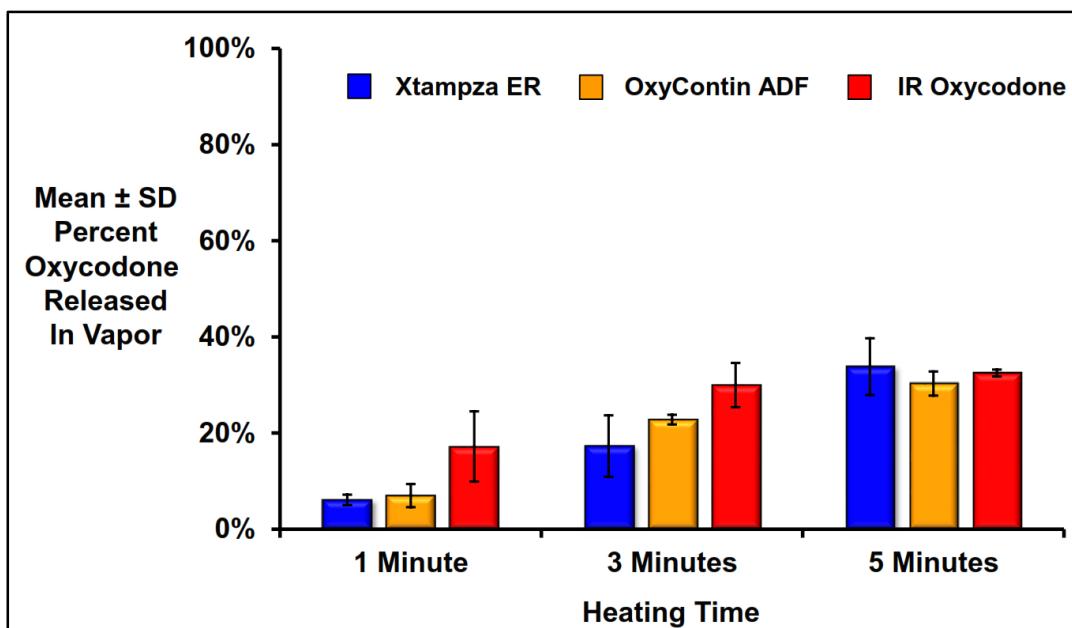
4.2% for original and reformulated OxyContin ADF, respectively) (Butler et al., 2008; Butler et al., 2013). Collegium developed a method to simulate the smoking of an oxycodone-containing product under controlled laboratory conditions using three different temperatures. In this controlled simulation, heat was applied continuously and the emitted vapors were collected continuously. Notably, this is a more efficient process than would be applied by an abuser, who in practice would not be capable of capturing all vapor via inhalation and would heat the product intermittently.

In the baseline condition, Xtampza ER, IR oxycodone, and OxyContin ADF had similar oxycodone recovery in the vapor condensate after 5 minutes (34% versus 33%, and 30% of label claim, respectively). IR oxycodone exhibited a marginally higher recovery of oxycodone in the condensate at the shorter time points of 1 and 3 minutes (Figure 10).

At the lowest temperature tested, all products released very little drug over three minutes, with IR oxycodone releasing the highest percent label claim (9.0%). At the highest temperature tested, the average percent of drug recovered in the vapor was similar for Xtampza ER and IR oxycodone (51% versus 43%, P=0.22); the percent recovered from OxyContin ADF was lower (36%). The duration of heating was extended in order to determine the amount of drug that could be recovered over prolonged exposure to heat. The observed trends when comparing between products were similar to results at the high temperature condition; note that the maximum average percent recovery in the vapor for Xtampza ER was 59% after 20 minutes due to significant drug degradation.

Based on the results of studies conducted and considering the prevalence of smoking for other available oxycodone containing products, smoking is not anticipated to be a preferred route of administration for Xtampza ER.

Figure 10: Mass (mg) Oxycodone Recovered in Vapor



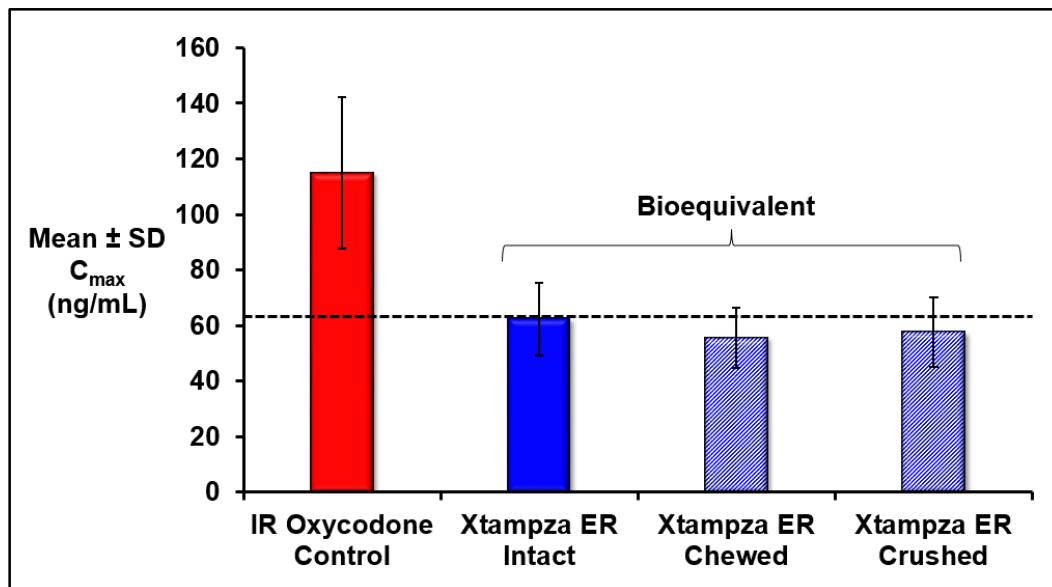
4.2 Category 2: Pharmacokinetics

4.2.1 Oral Administration of Manipulated Xtampza ER – Study 17

Study 17 was an open-label, randomized, active-controlled, NTX-blocked, single-dose, 7-period, crossover comparison study of 42 healthy subjects in the PK population. The study was designed to assess the impact of crushing or chewing on the PK profile of Xtampza ER. Treatment arms in the study evaluated Xtampza ER 40 mg dosed as either intact capsules or as crushed or chewed capsule contents in both fed and fasted states. Oxycodone IR solution (40 mg) in the fasted state was used as the comparator.

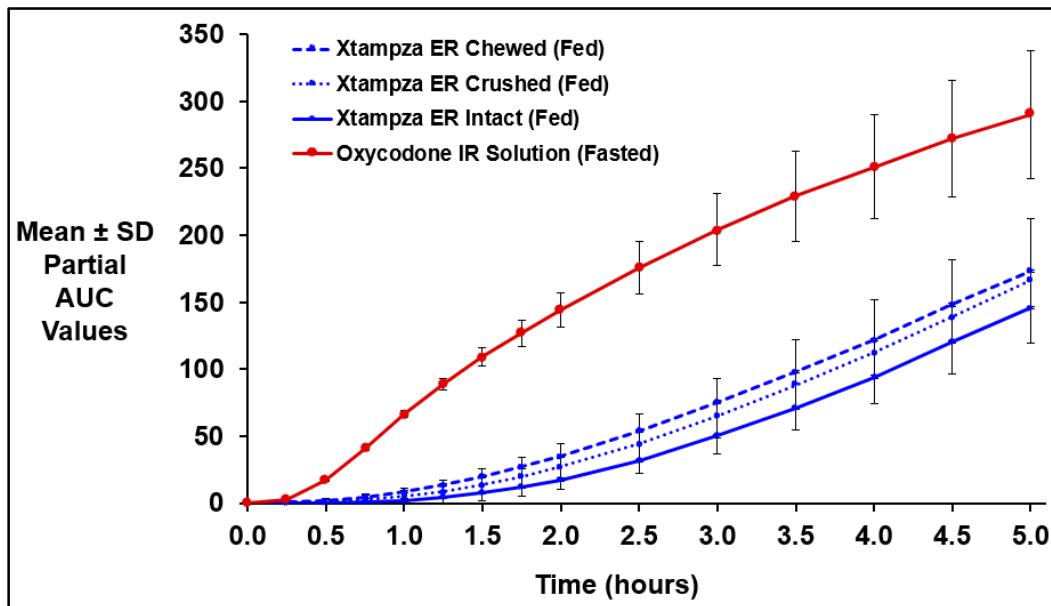
Figure 11 displays the mean C_{max} values for the Xtampza ER fed treatment arms, comparing manipulated Xtampza ER with intact Xtampza ER and IR oxycodone. Crushing or chewing Xtampza ER did not increase the mean C_{max} relative to intact Xtampza ER capsules (i.e., the dosage form intended to produce a therapeutic PK profile). Under fasted conditions, the C_{max} for all Xtampza ER treatment groups (intact, crushed, and chewed) fell below the C_{max} for intact, fed administration of Xtampza ER. These data illustrate very little difference between manipulated Xtampza ER treatments and intact Xtampza ER, showing that the product retains its ER characteristics upon physical manipulation.

Figure 11: Mean C_{max} Values under Fed Conditions – Study 17



Dashed line indicates intact Xtampza ER as a reference.

Figure 12 presents the partial AUC results through 5 hours post dose showing that both chewed and crushed Xtampza ER produced similar partial AUC values to intact Xtampza ER whereas the partial AUC for the oxycodone IR solution was markedly higher. These results further support that manipulation of Xtampza ER does not compromise the integrity of the ER formulation.

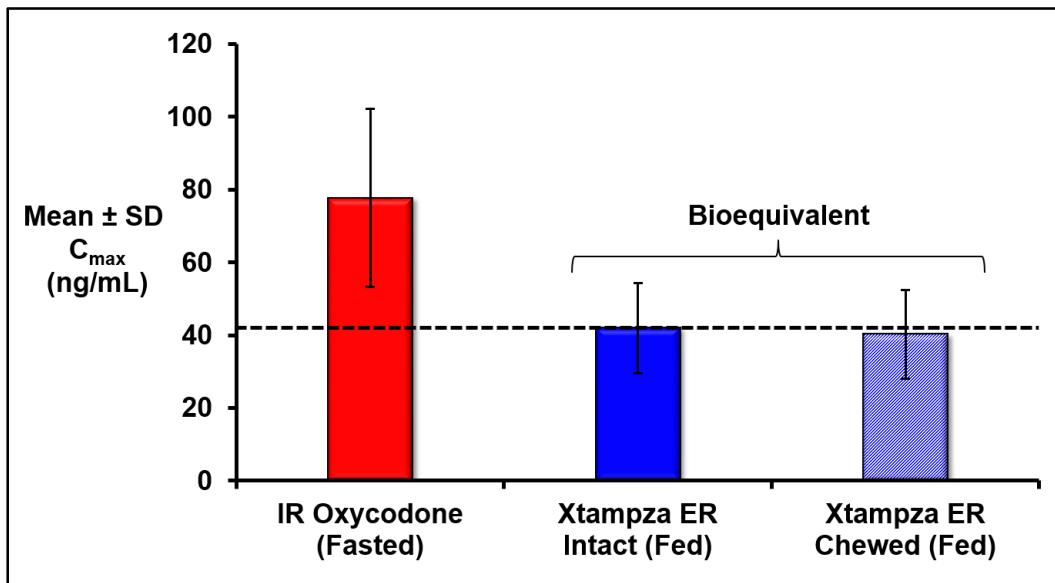
Figure 12: Mean Oxycodone Partial AUC Values – Study 17

The abuse quotient ($AQ = C_{max}/T_{max}$) has been suggested as a parameter to assess the rate of rise achieved in the blood when a formulation is manipulated by an abuser (Moorman-Li et al., 2012). By manipulating a formulation, an abuser seeks to maximize AQ, that is, increase C_{max} and decrease T_{max} . The mean AQ values for Xtampza ER intact and the manipulated treatment groups were similar in magnitude (ranging from 11.0 to 25.0 ng/mL/hr). The AQ value for oxycodone IR solution was the highest of all treatments (167.8 ng/mL/hr) and statistically greater than that of all Xtampza ER intact and manipulated groups ($P<0.0001$).

4.2.2 Oral Administration of Chewed Xtampza ER – Study 24

Study 24 was a non-NTX-blocked HAP study that also evaluated the PK of chewed and intact dosing of Xtampza ER in both the fed and fasted states compared with crushed IR oxycodone in solution in the fasted state (all doses were 40 mg).

The findings from the subjective PD assessments in this study are detailed in Section 4.3.3. The PK findings for this study were consistent with the findings from Study 17, and indicated that chewing (in the fed or fasted state) did not increase peak plasma exposure relative to the intact, fed treatment group. The mean C_{max} values for the Xtampza ER fed treatment arms are displayed in Figure 13, and demonstrate the similarity in the findings between Study 24 and Study 17; C_{max} values for Xtampza ER intact and chewed were bioequivalent and lower than IR oxycodone.

Figure 13: Mean C_{max} Values – Study 24

Dashed line indicates intact Xtampza ER as a reference.

4.2.3 Oral Administration of Manipulated Xtampza ER versus OxyContin ADF – Study 25

Study 25 was an open-label, randomized, active-controlled, NTX-blocked, single-dose, 5-period, crossover comparison study of 38 to 40 healthy subjects in the PK population (depending on the treatment arm). The study was designed to assess the impact of crushing Xtampza ER and OxyContin ADF on the PK profile. Treatment arms in the study evaluated Xtampza ER and OxyContin ADF (40 mg) dosed either as intact or crushed tablets/capsules in the fed state. Crushed IR oxycodone (40 mg) in the fed state was used as the comparator.

The crushed contents of Xtampza ER capsules were bioequivalent to intact Xtampza ER capsules, confirming that crushing the Xtampza ER microspheres does not alter oxycodone exposure (Figure 14, right panel). In contrast, crushed OxyContin ADF exhibited a plasma profile bioequivalent to crushed IR oxycodone tablets (Figure 14, left panel), indicating that a relatively simple physical manipulation can effectively convert OxyContin ADF into an IR formulation.

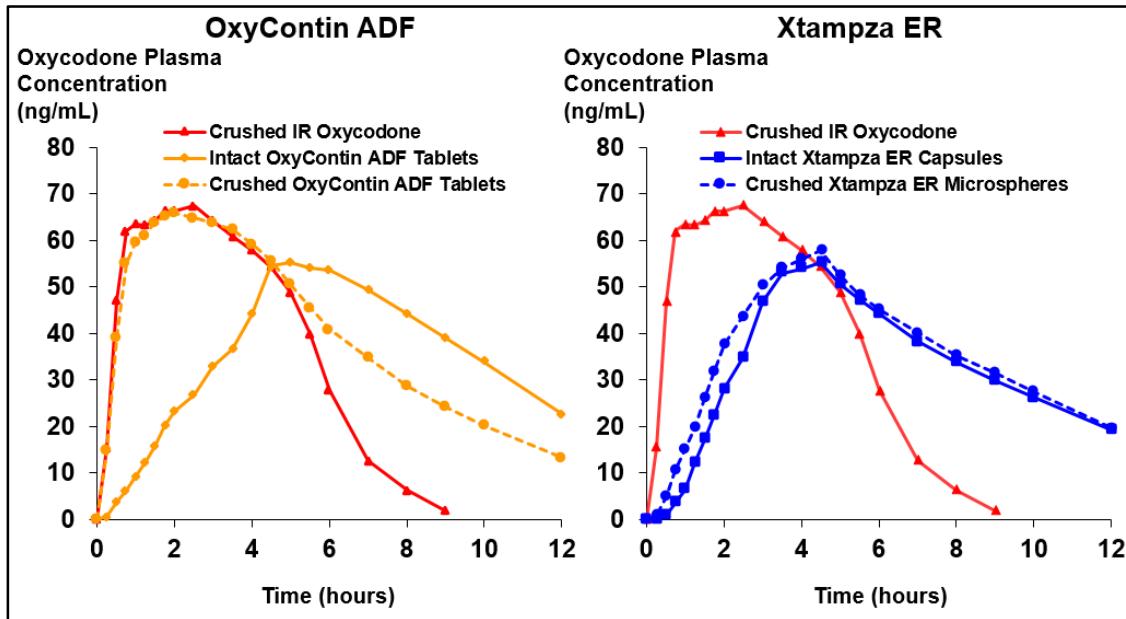
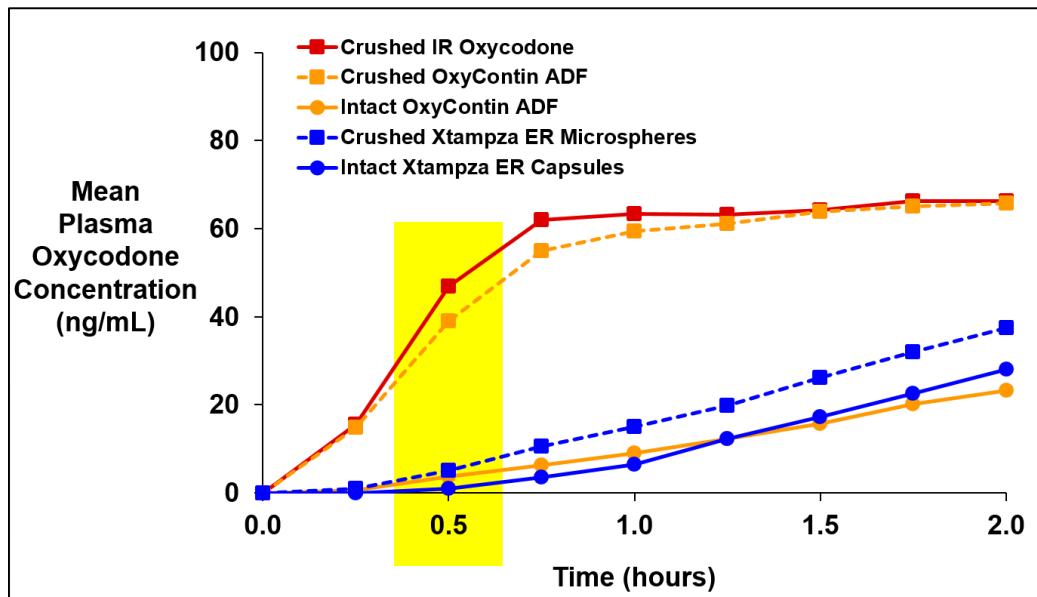
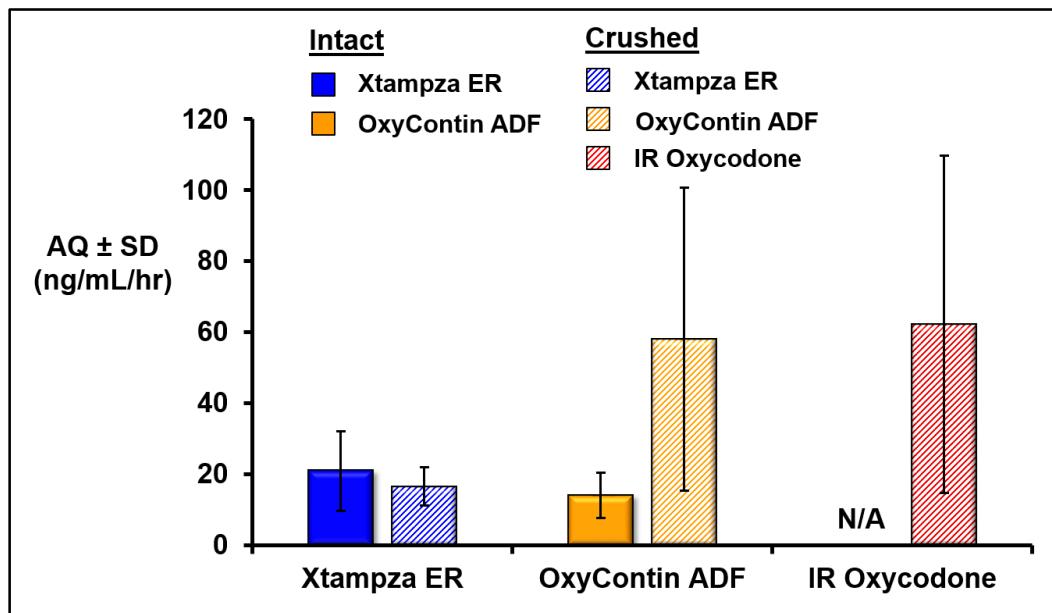
Figure 14: Mean Plasma Oxycodone Concentrations – Study 25

Figure 15 displays mean plasma oxycodone concentration levels for intact and manipulated Xtampza ER and OxyContin ADF in comparison to crushed IR oxycodone for the first 2 hours following dosing. Mean plasma concentrations for crushed OxyContin ADF were substantially greater than for crushed Xtampza ER during this critical early timeframe (e.g., plasma concentration at 0.5 hours was ~8 times higher), when abusers seek to maximize plasma exposure to obtain the desired euphoric effect.

Figure 15: Mean Plasma Oxycodone Concentration through 2 Hours – Study 25

Mean AQ values for the treatment arms in Study 25 are shown in Figure 16. AQ values for intact and crushed Xtampza ER (20.9 and 16.5 ng/mL/hr) and intact OxyContin ADF (14.0 ng/mL/hr) were similar, and substantially lower than the mean AQ value associated with crushed IR oxycodone (62.3 ng/mL/hr). Notably, crushed OxyContin ADF (58.1 ng/mL/hr) had an AQ value that was similar to that of crushed IR oxycodone.

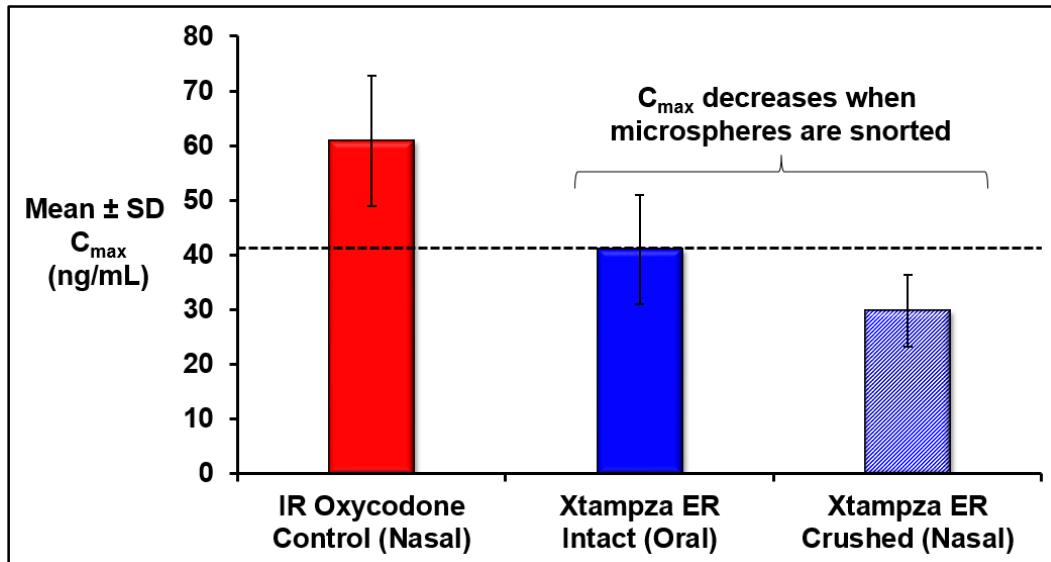
Figure 16: Abuse Quotient Values – Study 25



4.2.4 Nasal Administration of Manipulated Xtampza ER – Study 21

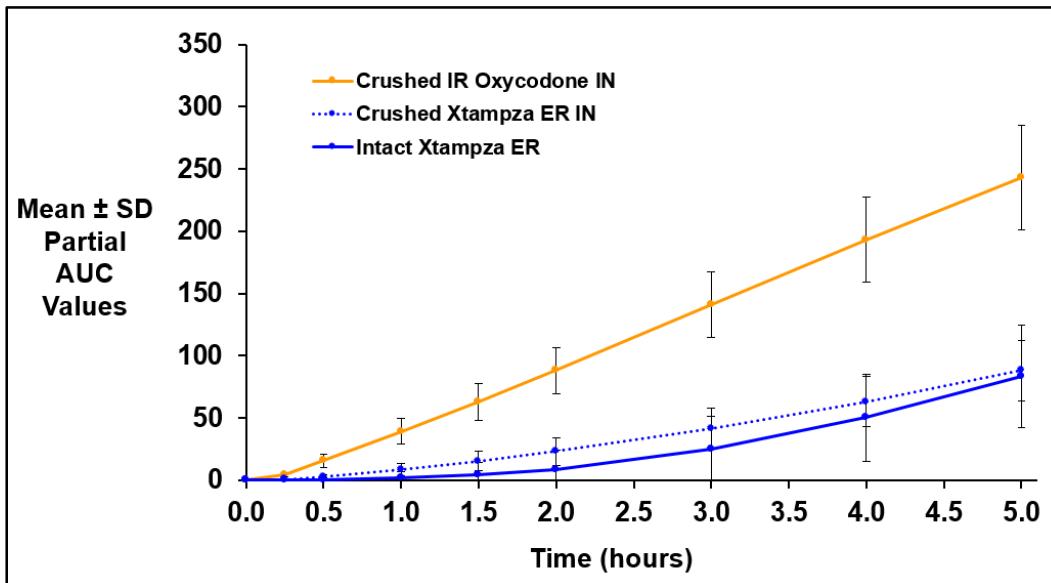
Study 21 was a double-blind, randomized, placebo- and active-controlled, 4-period, non-NTX-blocked, single-dose, crossover study of 36 nondependent, nontolerant, recreational drug abusers with a history of insufflating opioids in the PK population. The study evaluated the nasal abuse potential and PK of crushed Xtampza ER following nasal insufflation, intact Xtampza ER following oral administration, and crushed IR oxycodone tablets following nasal insufflation (all doses were 40 mg).

IN administration of crushed Xtampza ER resulted in approximately 30% lower peak exposure than Xtampza ER dosed intact and 50% lower peak exposure than crushed IR oxycodone dosed IN (Figure 17). The median T_{max} was equivalent when comparing crushed IN and intact administration of Xtampza ER (both 5.1 hours), which were both substantially longer than crushed IR oxycodone IN (2.6 hours). These data indicate that crushing and snorting Xtampza ER microspheres do not produce a rapid and high plasma exposure, which is sought by recreational drug abusers to achieve euphoria.

Figure 17: Mean C_{max} Values – Study 21

Dashed line indicates intact Xtampza ER as a reference.

Over the first 5 hours after dosing, the PAUC values for intact Xtampza ER taken orally and crushed Xtampza ER taken IN were similar in magnitude, but were substantially lower than the crushed IR oxycodone IN values (Figure 18).

Figure 18: Mean Partial AUC Values – Study 21

The mean AQ values for crushed Xtampza ER intranasal and intact Xtampza ER oral were comparable (6.2 and 8.6 ng/mL/hr). In contrast, the mean AQ value for crushed IR oxycodone

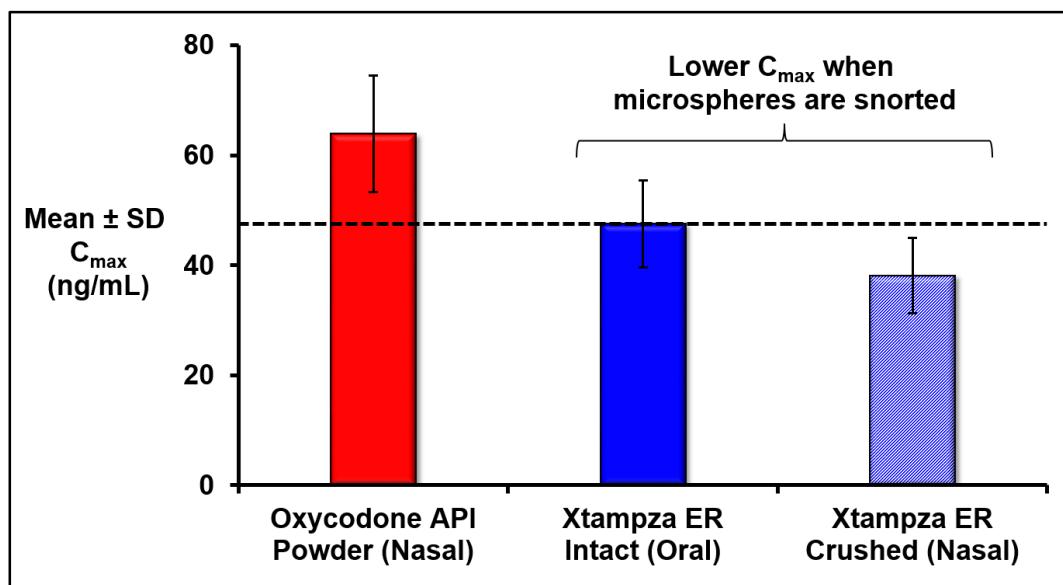
intranasal (69.6 ng/mL/hr) was approximately 11-fold higher than that for crushed Xtampza ER intranasal.

4.2.5 Nasal Administration of Manipulated Xtampza ER – Study 19

Study 19 was an open-label, randomized, active-controlled, 3-period, NTX-blocked, single-dose, crossover study of 13 nondependent, nontolerant, recreational drug abusers in the PK population with a history of insufflating opioids. The study evaluated the PK of crushed Xtampza ER following nasal insufflation, intact Xtampza ER following oral administration, and oxycodone active pharmaceutical ingredient (API) powder following nasal insufflation (all doses were 40 mg).

Study 19 results were similar to the findings of Study 21. IN administration of crushed Xtampza ER resulted in lower peak exposure than Xtampza ER dosed orally intact and lower peak exposure than crushed IR oxycodone IN (Figure 19).

Figure 19: Mean C_{max} Values – Study 19



Dashed line indicates intact Xtampza ER as a reference.

4.3 Category 3: Human Abuse Potential

4.3.1 General Methodology

Collegium conducted Study 21 and Study 24 to evaluate the PK and HAP of crushed Xtampza ER microspheres administered via the IN and oral routes, respectively. Both studies were randomized, double-blind, placebo-controlled, single-dose, crossover studies. The study populations consisted of subjects ages 18-55 who were non-dependent, non-tolerant, recreational drug abusers, and who used opioids for non-medical purposes on at least 10 occasions within the

last year and at least once in the 12 weeks before screening. Study 21 had the additional requirement that the subjects had a history of nasal administration of opioids.

The studies began with a Drug Discrimination Phase in which subjects had to pass a Naloxone Challenge Test, which was used to identify and disqualify opioid-tolerant subjects. Subjects who successfully completed this Naloxone Challenge Test were randomized to receive crushed IR oxycodone 20 mg and crushed placebo in a double-blind, random order. For Study 21, treatments were administered by the nasal route; for study 24, treatments were administered via the oral route. Subjects who could differentiate between the effects of a single dose of crushed IR Oxycodone 20 mg and placebo were then enrolled into the Double-blind Treatment Phase. Subjects who were intolerant to study treatments in the Drug Discrimination Phase (e.g., emesis after dosing) were discontinued from the study.

In addition to PK assessments (see results in Section 4.2.4 for Study 21 and Section 4.2.2 for Study 24), subjects underwent PD assessments including:

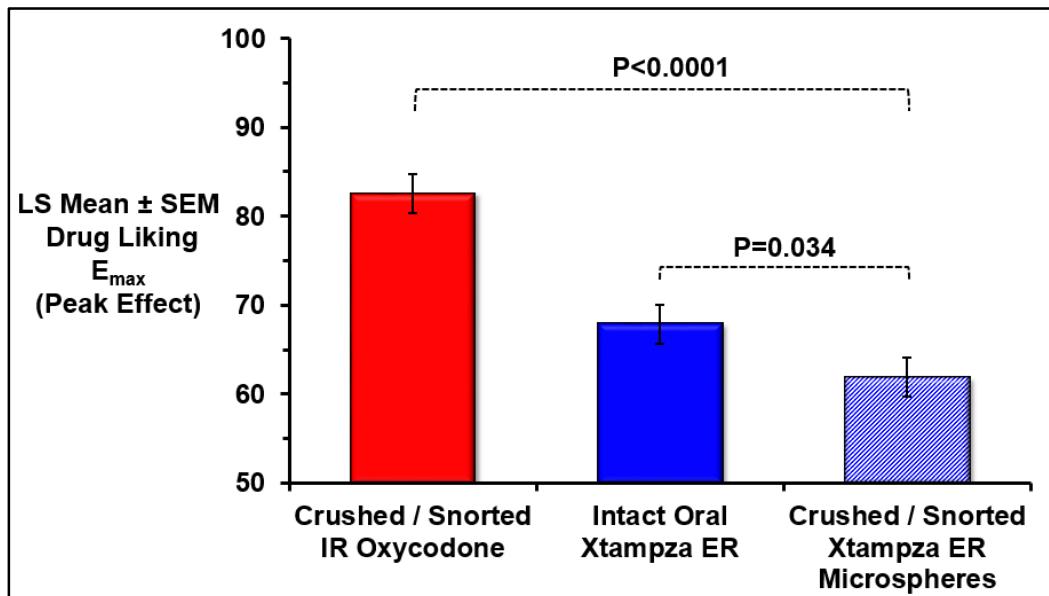
- Drug Effects Questionnaire (DEQ) to evaluate: drug liking, feeling high, any drug effects, good effects, bad effects, feel sick, nausea, sleepy and dizzy.
- Additional assessments: Ease of Snorting (nasal Study 21 only), Overall (Global) Drug Liking, the Addiction Research Center Inventory/Morphine Benzedrine Group (ARCI/MBG) scale, Take Drug Again Assessment, Price Value Assessment, and Pupilometry

The primary PD endpoint for the studies was the 0-100 mm bipolar visual analog scale (VAS) scale for Drug Liking (at the moment), for which a larger value indicates greater liking. The primary outcome measure was maximum (peak) PD effect (E_{max}) for Drug Liking.

4.3.2 Nasal Human Abuse Potential Study – Study 21

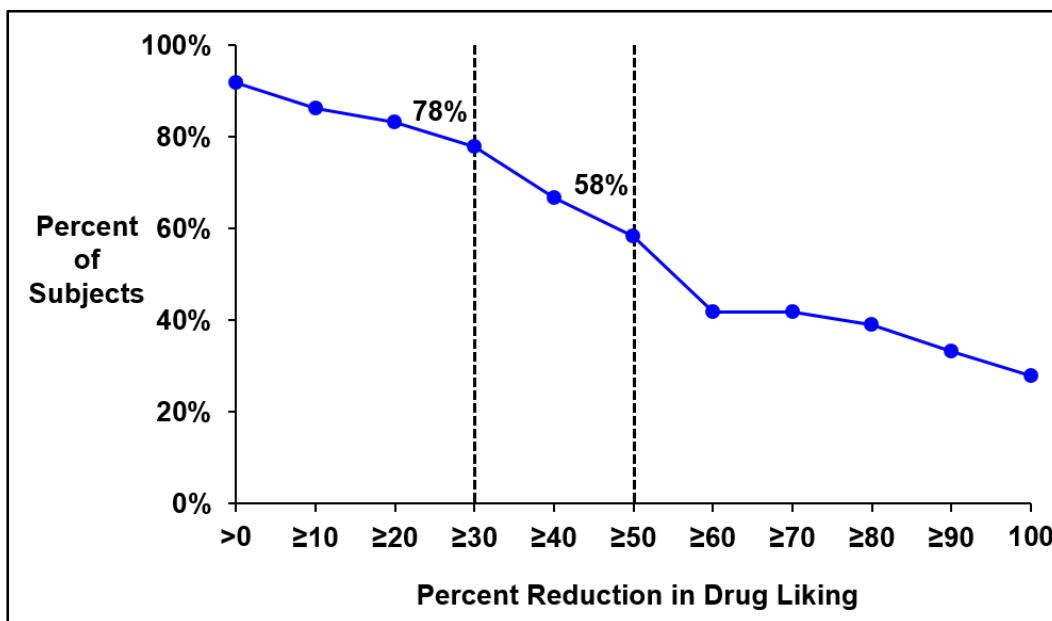
Study 21 was a double-blind, randomized, placebo- and active-controlled, 4-period, non-NTX-blocked, single-dose, crossover study of 36 nondependent, nontolerant, recreational drug abusers in the PK population with a history of insufflating opioids (n=36 for PD population). The study evaluated the nasal abuse potential and PK of crushed Xtampza ER following nasal insufflation, intact Xtampza ER following oral administration, and crushed IR oxycodone tablets following nasal insufflation (all doses were 40 mg).

The primary PD analysis for Study 21 was the comparison of the maximum Drug Liking (E_{max}) at the moment between crushed Xtampza ER IN versus the control crushed IR oxycodone IN. The primary endpoint was met (Figure 20). Drug liking E_{max} for crushed Xtampza ER IN and intact Xtampza ER dosed orally were significantly lower than the E_{max} for IN administration of crushed IR oxycodone ($P<0.0001$). Additionally, the Drug Liking E_{max} for crushed Xtampza ER IN was lower than for intact Xtampza ER dosed orally ($P=0.034$). For both Xtampza ER treatments (crushed IN and intact oral), the time to maximum effect (TE_{max}) was significantly longer than for crushed IR oxycodone IN ($P\leq0.05$).

Figure 20: Maximum Drug Liking (E_{max}) – Study 21


SEM = standard error of the mean

Analysis of the percentage reduction in Drug Liking VAS score for crushed Xtampza ER IN relative to crushed IR oxycodone IN demonstrated a robust response for individual subjects, with 78% and 58% of subjects showing at least a 30% or 50% reduction, respectively (Figure 21).

Figure 21: Percentage Reduction Profile for E_{max} of Drug Liking VAS for Crushed Xtampza IN versus Crushed IR Oxycodone IN – Study 21


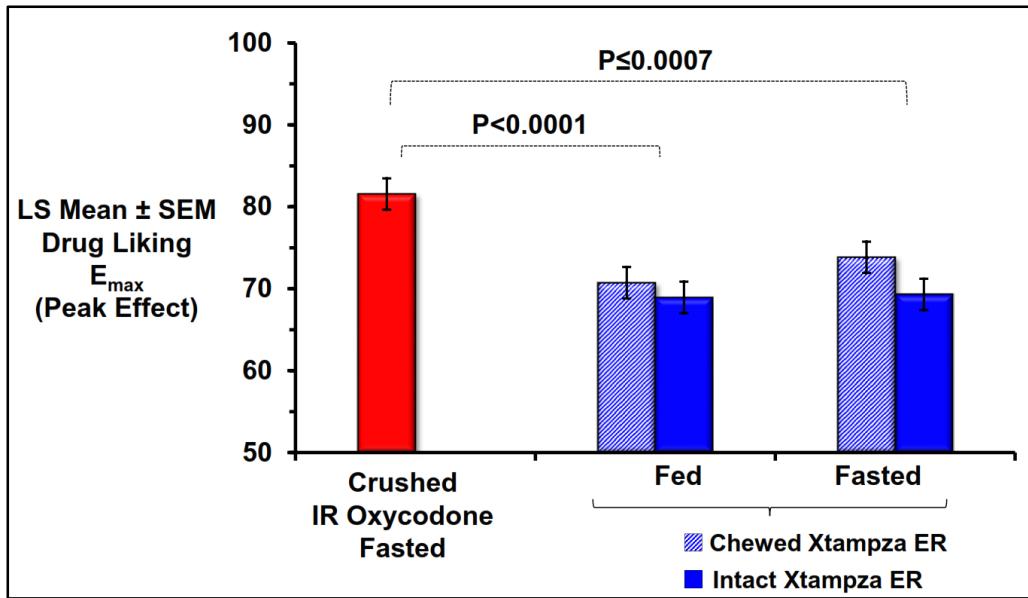
Results of secondary endpoint analyses were consistent with the findings for the primary analysis. For each measure of crushed Xtampza ER IN and intact oral administration, significantly lower E_{max} values were found relative to IR oxycodone for DEQ any drug effects, good drug effects, high, nausea, sleepy, and dizzy; Overall Drug Liking, Take Drug Again Assessment, ARCI-MBG, Price Value Assessment and pupillometry values were also lower.

4.3.3 Oral Human Abuse Potential Study – Study 24

Study 24 was a double-blind, randomized, placebo- and active-controlled, 6-period, non-NTX-blocked, single-dose cross-over study of 47 nondependent, nontolerant, recreational drug abusers in the PK population with a history of opioid abuse (n=38 for PD population). that evaluated the oral abuse potential and PK of chewed and intact dosing of Xtampza ER in both the fed and fasted states compared with crushed IR oxycodone in solution in the fasted state (all doses were 40 mg).

The primary PD analyses for Study 24 were the comparison of the maximum Drug Liking (E_{max}) at the moment between chewed Xtampza ER (fed and fasted) versus the control crushed IR oxycodone in solution. The primary endpoints were met (Figure 22). Drug liking E_{max} values for chewed Xtampza (both fed and fasted) were significantly lower than the E_{max} for crushed IR oxycodone ($P \leq 0.0007$). Additionally, the Drug Liking E_{max} values for intact Xtampza (both fed and fasted) were lower than for crushed IR oxycodone ($P < 0.0001$). All Xtampza ER treatments (crushed and intact, fed and fasted) had significantly longer time to maximum effect (TE_{max}) than crushed IR oxycodone ($P < 0.0001$).

Figure 22: Maximum Drug Liking (E_{max}) – Study 24

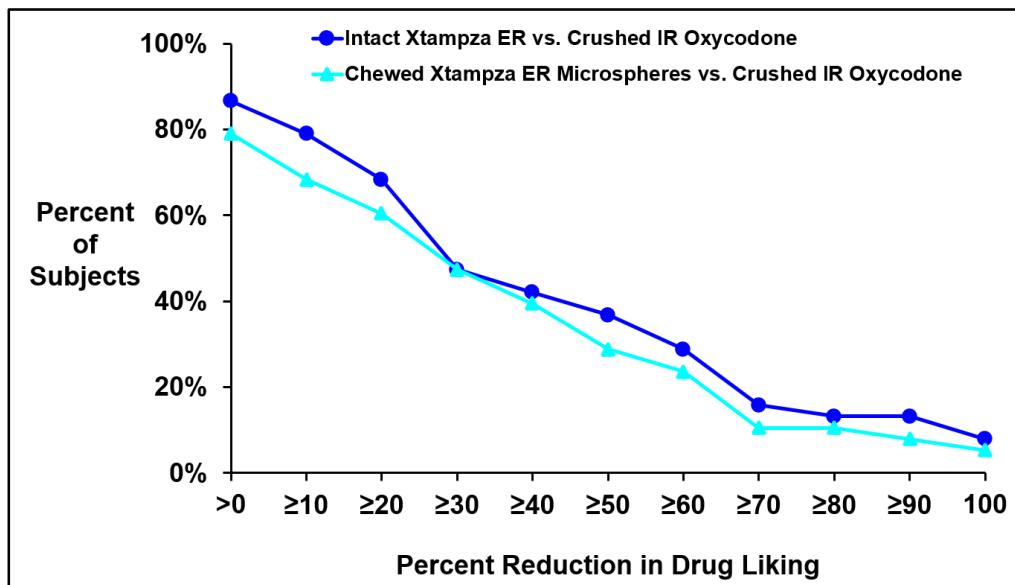


SEM = standard error of the mean

The percent reduction profiles for E_{max} of Drug Liking VAS comparing intact or chewed Xtampza ER in the fed state with crushed IR oxycodone in the fasted state is presented in Figure

23. This figure shows similar profiles in percent reduction of drug liking relative to crushed IR oxycodone for Xtampza ER whether it is administered chewed or intact in the fed state. Lower drug liking relative to IR oxycodone was also true for chewed and intact administration in the fasted state.

Figure 23: Percent Reduction Profiles for E_{max} of Drug Liking VAS for Chewed and Intact Xtampza ER versus Crushed IR Oxycodone – Study 24



Secondary endpoints were analyzed for the primary comparisons in the study. For the comparison of chewed Xtampza ER fed to crushed IR oxycodone, significantly lower E_{max} values were found for DEQ any drug effects, good drug effects, high, bad drug effects, sick, sleepy, and dizzy; Overall Drug Liking, ARCI/MBG, and Price Value Assessment values were also lower. For the comparison of chewed Xtampza ER fasted to crushed IR oxycodone, significantly lower E_{max} values were found for DEQ any drug effects, good drug effects, high, sleepy, and dizzy; ARCI/MBG, and pupillometry values were also lower.

4.4 Abuse Deterrence Evaluation Conclusions

Overall, data from laboratory studies, PK studies, and HAP studies, including comparative studies to OxyContin ADF and IR oxycodone, demonstrated the robust abuse-deterrant properties of Xtampza ER. Based on these studies, it is anticipated that Xtampza ER has the potential to be more resistant to manipulation and abuse than currently available formulations of oxycodone.

5 FOOD AND ALCOHOL EFFECTS

Summary

- In a single-dose, naltrexone (NTX)-blocked study (Study 15), bioavailability of Xtampza ER was similar to OxyContin ADF when dosed with any amount of food, but was lower under fasted conditions. Xtampza ER will, therefore, be labeled “take with food”.
- The potential effects of noncompliance with “take with food” labeling instructions were examined under more clinically relevant conditions (i.e., steady-state conditions and administration of Xtampza ER without NTX block, which is known to influence opioid absorption).
 - A steady state NTX-blocked study (Study 18) that simulated regular noncompliance with the labeling instructions for food (i.e., fasted AM dose, fed PM dose) found that plasma fluctuations and overall oxycodone plasma exposure were similar for Xtampza ER and OxyContin ADF.
 - A single-dose, non-NTX-blocked study (Study 24) demonstrated that the magnitude of the food effect with Xtampza ER was substantially diminished without NTX block. The overall plasma exposure as measured by AUC_{inf} was BE for the fed and fasted states without NTX.
 - Within subject peak exposure differences between the fed and fasted states were analyzed for Studies 15, 18, and 24; maximum ratios of fed-to-fasted C_{max} were identified. The more clinically relevant conditions of steady-state dosing (Study 18) and dosing without NTX block (Study 24) produced meaningfully lower maximum ratios than observed in the single-dose, NTX-blocked study.
- A review of published data showed that the food effect of Xtampza ER without NTX block is within the range of other approved opioid products.
- The pivotal, Phase 3 study (Study 08), evaluated the effects of food intake on the safety and efficacy of Xtampza ER.
 - Food intake data were collected via electronic diary with every dose in the study (>65,000 doses).
 - An independent adjudication committee found no relationship between SAEs or severe AEs related to Xtampza ER that were related to food intake.
 - Post-hoc analyses revealed no association between specific meal patterns with the incidence of all AEs, AEs related to Xtampza ER, or opioid-related specific AEs.
 - Meal pattern analyses also found no relationship between the amount of food consumed and the efficacy of Xtampza ER.
- Overall, the Xtampza ER clinical development program supports a “take with food” label; the food effect with Xtampza ER is not expected to produce any clinically relevant consequences.
- Co-administration of Xtampza ER with 20% and 40% alcohol in the fasted state did not lead to higher exposures than 0% alcohol in a fed state (i.e., Xtampza ER taken as directed), suggesting no evidence of “dose dumping” in the presence of alcohol.

5.1 Approach to Assessing the Effect of Food on Xtampza ER

As detailed in this section of the briefing book, single-dose, NTX-blocked PK studies on Xtampza ER have identified an effect of food on bioavailability. As the magnitude of this food effect is greater than the OxyContin ADF reference product, Collegium has conducted multiple evaluations aimed at assessing whether the food effect is likely to be clinically meaningful. These evaluations are detailed in the following sections:

- Pharmacokinetic Evaluation of Food Effect
 - Single-dose, NTX-blocked study results (Section 5.2.2)
 - Steady state, NTX-blocked study results (Section 5.2.3)
 - Single-dose, non-NTX-blocked study results (Section 5.2.4)
- Food Effects in Other Opioid Products (Section 5.2.6)
- Evaluation of the Influence of Food in the Pivotal, Phase 3 Safety and Efficacy Study
 - Safety and Food Intake at Dosing (Section 5.3.1)
 - Efficacy and Food Intake at Dosing (Section 5.3.2)
- Conclusion (Section 5.4)

5.2 Pharmacokinetic Evaluation of the Food Effect

5.2.1 Introduction to Relative Bioavailability and Food Effect Studies

The PK characteristics of Xtampza ER capsules have been evaluated in relative bioavailability studies using OxyContin ADF as the reference product. A single-dose, NTX-blocked study was conducted according to FDA recommendations to assess relative bioavailability and food effects. Additionally, to characterize more clinically relevant conditions, the effect of food was studied in a steady-state study (also with NTX block) and a single-dose study without NTX block. The studies conducted and their designs are presented in Table 10.

Table 10: Studies Assessing Relative Bioavailability and Food Effect

Attribute	Study 15	Study 18	Study 24 ^b
Design	Single-dose, NTX Block	Steady-state, NTX Block	Single-Dose, No NTX Block
N^a	48	39	47
Dosage Strength	40 mg	40 mg	40 mg
Treatment Groups	<ul style="list-style-type: none">• Xtampza ER in the fasted state• Xtampza ER with a low-fat, low-calorie (LFLC) meal• Xtampza ER with a medium-fat, medium-calorie (MFMC) meal• Xtampza ER with a high-fat, high-calorie (HFHC) meal• OxyContin ADF in the fasted state• OxyContin ADF with a HFHC meal	<ul style="list-style-type: none">• Xtampza ER for all doses with a HFHC meal• OxyContin ADF for all doses with a HFHC meal• Xtampza ER in the fasted state for AM doses and with a HFHC meal for PM doses• OxyContin ADF in the fasted state for AM doses and with a HFHC meal for PM doses	<ul style="list-style-type: none">• Xtampza ER in the fasted state• Xtampza ER with a HFHC meal

NTX=Naltrexone; ^a Indicates number of subjects in the PK population; ^b Study 24 had additional treatment arms to assess human abuse potential; only treatment arms relevant to assessment of food effect shown

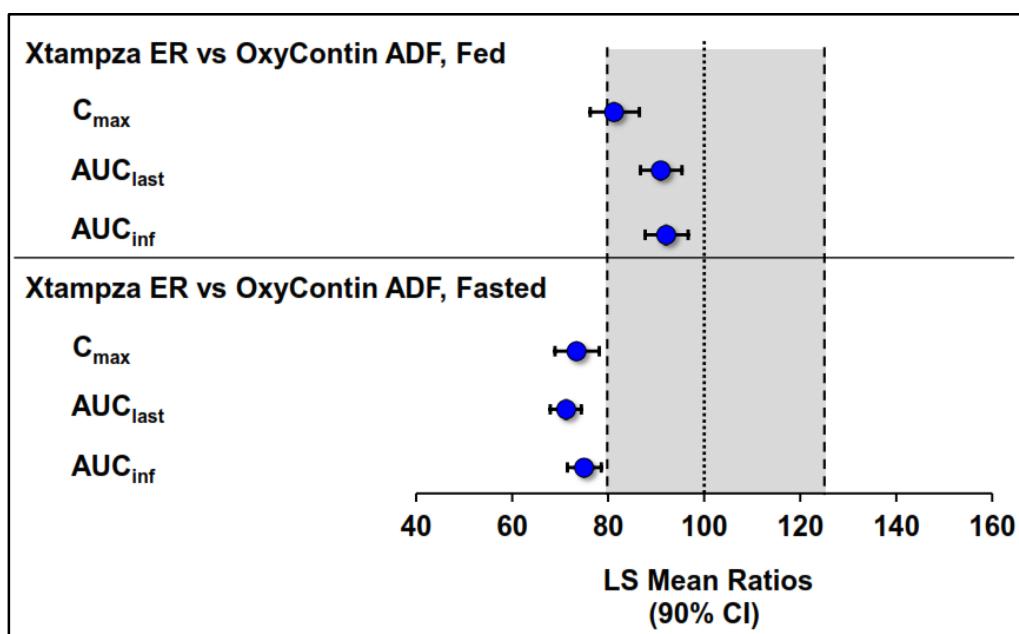
5.2.2 Single-Dose, NTX-Blocked Study – Study 15

5.2.2.1 Bioavailability of Xtampza ER Relative to OxyContin ADF

The PK characteristics of Xtampza ER capsules were evaluated in relative BA studies using OxyContin ADF as the reference product. In the single-dose, NTX-blocked study, the PK profiles for Xtampza ER and OxyContin ADF were similar when dosed with a HFHC meal; under fasted conditions, the peak and overall exposure following Xtampza ER administration was lower than for OxyContin ADF. These findings are shown graphically in Figure 24, which display the ratios and 90% CIs for C_{max} , AUC_{last} and, AUC_{inf} .

Per FDA guidelines, PK profiles are considered BE if the 90% CIs are contained within 80%-125%. As the overall exposure (AUC) for Xtampza ER is lower than OxyContin ADF under fasted conditions, but BE under fed conditions, the proposed label for Xtampza ER instructs patients to take Xtampza ER with food in order to achieve an exposure equivalent to OxyContin ADF at the same dose.

Figure 24: Bioequivalence Parameters for Xtampza ER Relative to OxyContin ADF under Fed (HFHC) and Fasted Conditions, Single-Dose with NTX Block – Study 15



5.2.2.2 Effect of Meal Size on Xtampza ER Bioavailability

The single-dose, NTX-blocked Study 15 evaluated 3 fed conditions in addition to fasted administration. The fed conditions were:

- High-fat, high calorie (HFHC, ~900 kcal)
- Medium-fat, medium-calorie (MFMC, ~400 kcal)
- Low-fat, low-calorie (LFLC, ~100 kcal)

These conditions were intended to bracket the range of how a patient may interpret the take with food instruction, characterizing a heavy meal down to consumption with a very small meal or snack; in this case, a single piece of toast and one cup of decaffeinated coffee.

The results of the study demonstrated that when consumed with any quantity of food, Xtampza ER bioavailability (C_{max} and AUC) fell within the range of OxyContin ADF when dosed fasted or with a HFHC meal (Table 11). Consequently, when dosed with food, Xtampza ER provides exposures similar to OxyContin ADF when dosed per its label instruction (with or without food).

Table 11: Bioavailability of Xtampza ER with Food Relative to OxyContin ADF – Study 15

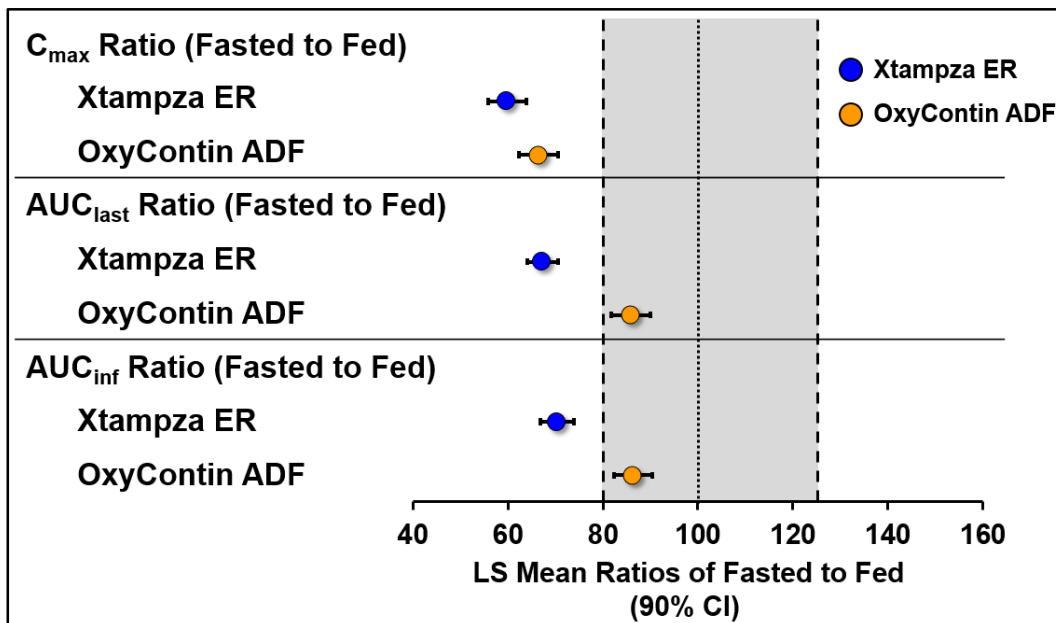
Xtampza ER Administration Condition	Comparison to OxyContin ADF
Fasted	Exposure lower than OxyContin ADF fasted (C_{max} and AUC)
LFLC	Bioequivalent to OxyContin ADF fasted (C_{max} and AUC)
MFMC	Bioequivalent to OxyContin ADF HFHC (C_{max} and AUC)
HFHC	AUC bioequivalent to OxyContin ADF HFHC; similar C_{max}

AUC = area under the concentration-time curve; C_{max} = maximum plasma concentration; HFHC = high-fat, high-calorie; LFLC = low-fat, low-calorie; MFMC = medium-fat, medium-calorie

5.2.2.3 Food Effects of Xtampza ER and OxyContin ADF

In addition to comparing the bioavailability of Xtampza ER to OxyContin ADF, the effect of food was evaluated by comparing HFHC versus fasted administration for each respective product in the single-dose, NTX-blocked Study 15. Both Xtampza ER and OxyContin ADF exhibited directionally similar effects of food on bioavailability, as exposure was lower for both products when dosed fasted than fed (Figure 25). The peak exposures (C_{max}) were outside BE limits for both products when comparing fasted to fed administration. The effect of food on overall exposure (AUC) was more pronounced for Xtampza ER than for OxyContin ADF; fed and fasted AUC did not fall within BE limits for Xtampza ER.

Figure 25: Bioequivalence Parameters for Xtampza ER and OxyContin ADF for Fasted to Fed (HFHC) States, Single-Dose with NTX Block – Study 15



5.2.2.4 Limitations of Single-Dose Study 15

Several key limitations and clinical considerations with respect to the results of Study 15 should be noted. First, single-dose studies are not representative of the clinical scenario under which Xtampza ER will be used. Therefore, a study conducted under steady-state conditions, which is a surrogate for repeated dosing over an extended period of time for the management of chronic pain, provides a more appropriate estimate of the food effect under more clinically relevant conditions. These dosing conditions were evaluated in Study 18 (Section 5.2.3), which also considered the effects of regular noncompliance with the proposed “take with food” label (i.e., taking the product fasted at every other dose for 5 days).

Secondly, NTX is known to influence the absorption of opioids (Bashaw et al., 1995; Sathyan et al., 2007; NDA Review 021610; NDA Review 021611), including oxycodone (Purdue Pharma L.P., 2014), so a study conducted without NTX block is relevant to determine the true magnitude of the food effect with Xtampza ER. A single-dose study, Study 24 (Section 5.2.4), evaluated the PK of fed and fasted dosing of Xtampza ER without NTX block.

Finally, an important clinical consideration is whether noncompliance with the food instruction leads to any clinical consequences for safety and efficacy. Thus, the multiple-dose, non-NTX-blocked, Phase 3 study was designed to collect data on food intake at every dose throughout the trial (up to ~135 days of treatment) in order to assess any potential relationships between the frequency and amount of food consumed on pain (i.e., efficacy) and adverse events (i.e., safety). The results of these analyses are detailed in Section 5.3.1.

5.2.3 Steady State, NTX-Blocked Study – Study 18

5.2.3.1 “Compliant” Dosing – Dosing with Food During AM and PM Administration

The plasma profiles at steady state for both Xtampza ER and OxyContin ADF were characterized when the products were administered with food every 12 hours. This comparison provides data for the plasma exposure of Xtampza ER when taken per the proposed label instruction. Under these conditions, the steady-state profiles on Day 5 for Xtampza ER and OxyContin ADF were virtually identical and BE (Table 12).

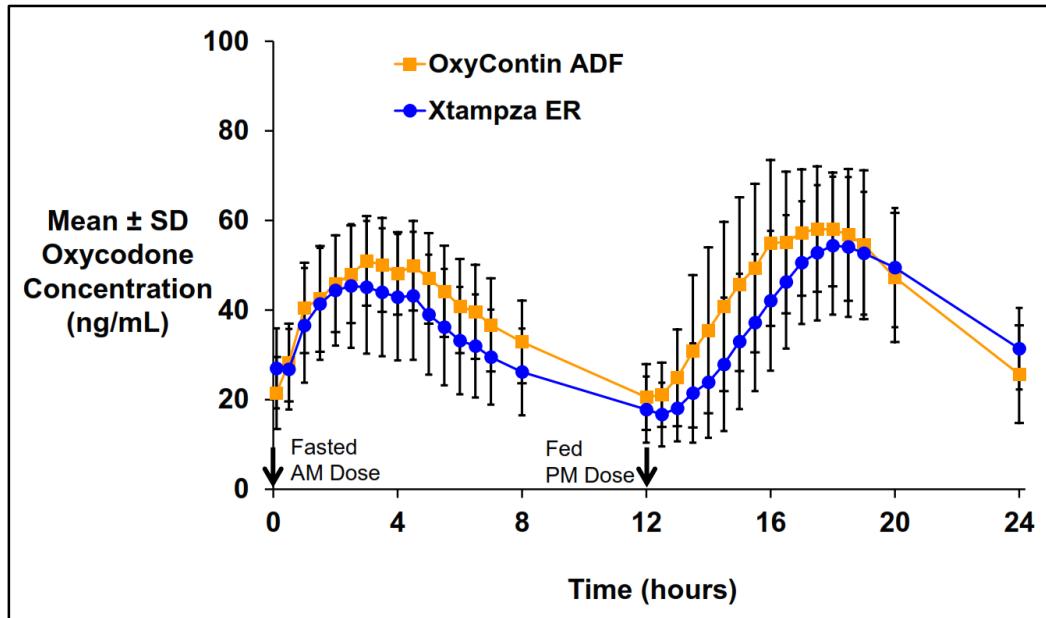
Table 12: Summary of PK Parameters for Xtampza ER and OxyContin ADF, Steady-State Fed Dosing – Study 18

PK Parameter	Xtampza ER	OxyContin ADF
C _{max} (ng/mL), mean ± SD	77.7 ± 23.6	77.1 ± 17.8
T _{max} (hr), median (range)	3.5 (1.0 – 5.5)	4.5 (1.0 – 6.5)
C _{min} (ng/mL), mean ± SD	21.3 ± 7.1	21.2 ± 6.4
AUC _{tau} (hr*ng/mL), mean ± SD	511 ± 116	532 ± 118
% PTF (12-hour dosing interval)	134 ± 35.8	127 ± 18.9

% PTF = Percentage of peak-trough fluctuation within a dosing interval

5.2.3.2 “Non-compliant” with Take with Food Instruction – Alternating Fasted Dosing (AM) and Fed Dosing (PM)

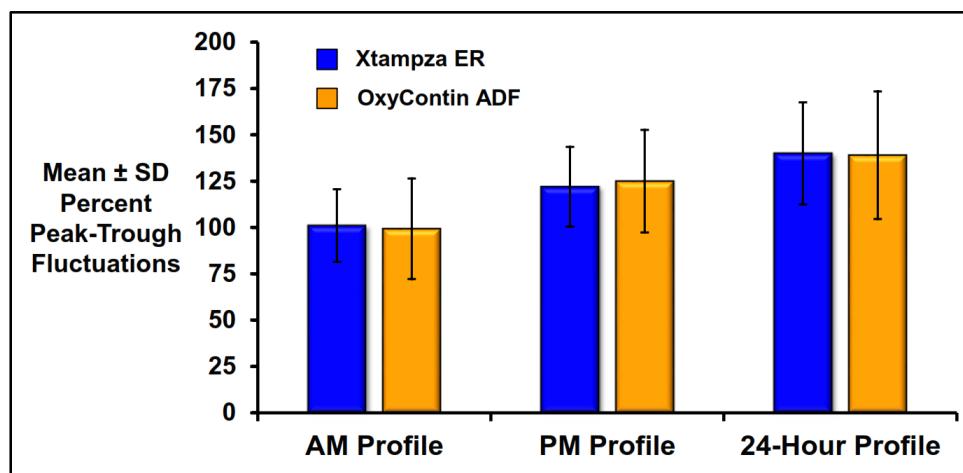
In order to simulate a situation in which patients are non-compliant with the take with food instruction, the plasma profile of Xtampza ER was characterized after 5 days of dosing fasted in the morning and fed in the evening and was compared with OxyContin ADF under the same conditions. Alternating fasted and fed doses produced steady-state concentration-time profiles that were BE for Xtampza ER and OxyContin ADF when assessed over the PM dosing interval and nearly bioequivalent when assessed over the AM dosing period (Figure 26).

Figure 26: Mean Concentrations of Oxycodone After Fed and Fasting Dosing – Study 18

The variation in plasma exposure for the steady-state profiles was assessed in two ways. First, the steady-state peak-to-trough fluctuations (%PTF) were calculated. Steady-state %PTF provides a measure of the range in plasma concentrations in a given time interval. Figure 27 displays the %PTF values for Xtampza ER and OxyContin ADF during the 12-hour AM and PM dosing intervals as well as over the full 24-hour period. The %PTF values were nearly identical between the 2 products. Secondly, the C_{max} associated with the PM dose was compared with the C_{max} associated with the AM dose. For both products, the mean ratio of PM (fed) C_{max} to AM (fasted) C_{max} was 1.3. The ratios calculated within individual subjects were also comparable between the two products with an individual subject maximum ratio of 2.0 for Xtampza ER and 2.3 for OxyContin ADF.

Therefore, the results of steady-state, NTX-blocked Study 18 suggest that the food effect observed with Xtampza ER in the single-dose, NTX-blocked Study 15 is substantially diminished under more clinically relevant, steady-state, albeit still NTX-blocked conditions. Further, non-compliance with “take with food” (even at every other dose) does not produce plasma fluctuations greater than that of OxyContin ADF.

Figure 27: Steady-State Percent Peak-Trough Fluctuations, Alternating Fasted and Fed Dosing – Study 18

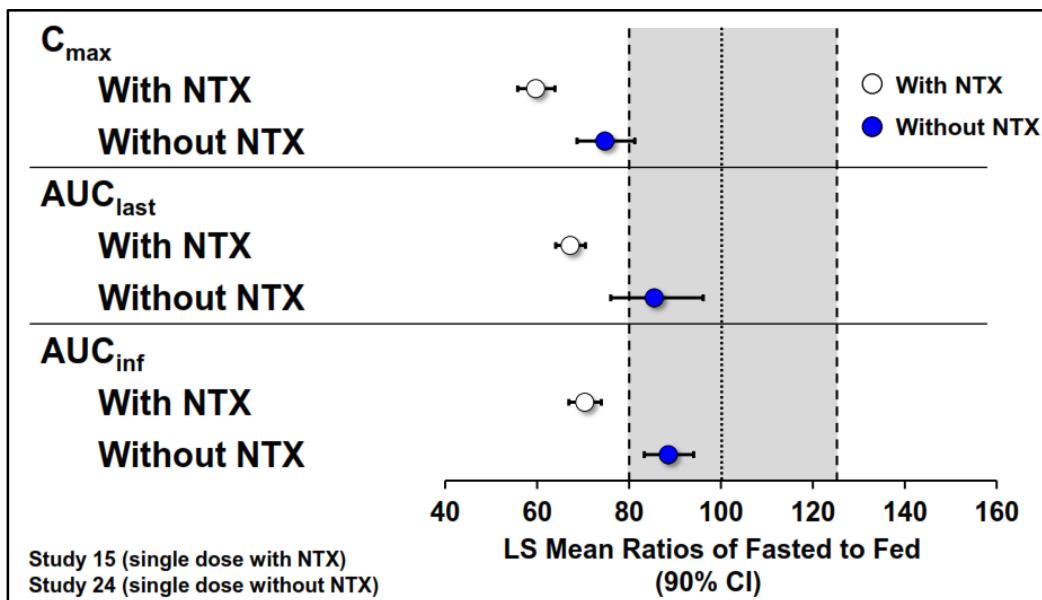


5.2.4 Single-Dose, Non-NTX-Blocked Study – Study 24

Study 24 was a single-dose, non-NTX-blocked oral HAP study of subjects who were nondependent, nontolerant, recreational drug abusers. While the primary design of the trial was to evaluate oral HAP, the study collected PK data for intact Xtampza ER in both the fed and fasted states, which provides data on the effect of food on Xtampza ER in the absence of NTX.

Results showed that in the absence of NTX block, the food effect is substantially diminished when compared with the results obtained under an NTX block; the ratios for all PK parameters are closer to 100% when comparing fasted to fed administration. In fact, AUC_{inf} fell within bioequivalence limits in the absence of NTX (Figure 28).

Figure 28: Effect of Food on Xtampza ER Bioavailability with and without Naltrexone



The fact that Xtampza ER absorption is affected by co-administered with NTX is anticipated based on data in the peer-reviewed literature and other publically-available data regarding ER opioids. Morphine co-administered with NTX leads to increases in C_{max} of 15% and AUC increases by 23% ([Bashaw et al., 1995](#)). Hydromorphone dosed with NTX increased C_{max} by 39%, AUC was unchanged, and the apparent half-life decreased by approximately 4.5 hours ([Sathyan et al., 2007](#)). A crossover conducted examined the influence of NTX on oxymorphone exposure, and found that NTX increased C_{max} by 38% ([NDA Review 021610](#); [NDA Review 021611](#)). Regarding oxycodone, the prescribing information for OxyContin states “data obtained while subjects received naltrexone, which can enhance absorption” ([Purdue Pharma L.P., 2014](#)).

While there are several reports of NTX affecting opioid exposure, there is less available information on the potential impact of NTX on food effects. No direct studies on the impact of NTX on oxycodone absorption with and without food are available. However, a cross-study comparison of publically-available studies conducted on the original OxyContin formulation (non-abuse deterrent) suggest that NTX increases the magnitude of the observed food effect; without NTX no food effect was observed whereas with NTX fed exposure was greater than fasted exposure (C_{max} increased by 27% and AUC increased by 20% with food) ([NDA Review 022272](#); [NDA Review 020553](#)).

The available data provides support for the findings of Study 24 and together suggest that NTX has an impact on Xtampza ER bioavailability, and further, that the relative impact depends on whether NTX is co-administered in fed or fasted conditions. Consequently, while NTX-blocked studies are useful for comparing relative bioavailability between products in the same fed or fasted state, the absolute magnitude of a food effect under actual clinical-use conditions must be considered without NTX.

5.2.5 Individual Subject C_{max} Ratios Comparing Fed-to-Fasted Administration

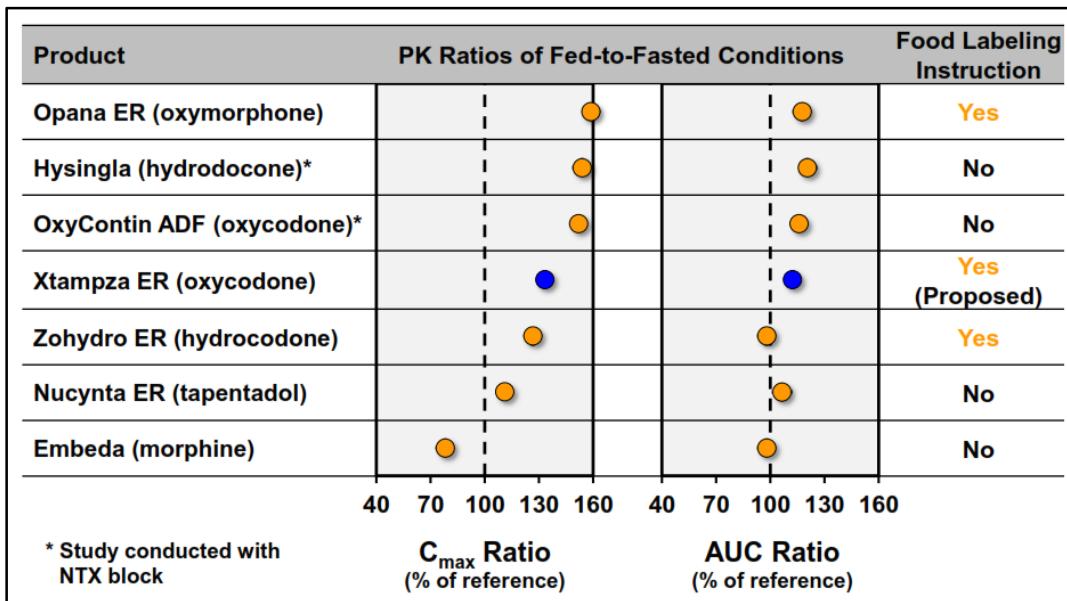
For Studies 15, 18 and 24, the difference in C_{max} between fed and fasted conditions within individual subjects was examined for Xtampza ER. Comparing fed-to-fasted administration, the highest C_{max} ratio in Study 15 (single-dose, NTX block) was 3.8. In more clinically relevant studies such as Study 18 (steady-state dosing with alternating fasted and fed administration, NTX block), the highest observed individual subject ratio with Xtampza ER was 2.0 (versus 2.3 for OxyContin ADF). In study 24 (single-dose, no NTX block) the highest observed individual subject ratio was 2.1. Thus, dosing under more clinically relevant conditions reduced the within-subject difference in peak exposure between fed and fasted states when compared with single-dose, NTX-blocked administration.

5.2.6 Food Effects in Other Opioid Products

When compared with other opioid products, the food effect of Xtampza ER without NTX block falls within the range of other opioids (Figure 29). The magnitude of the food effect is lower than for Opana ER (oxymorphone) and Hysingla (hydrocodone) which was recently FDA approved. Opana ER was studied without NTX block, and has a label with regard to food intake to take fasted. Hysingla was studied with NTX block, so possible confounds are unknown, however, it does not have a label with respect to food intake. As such, the food effect observed with

Xtampza ER is not unique, and food effects of even greater magnitude have been handled via labeling for another opioid product (i.e., Opana ER) in past.

Figure 29: PK Characteristics of Food Effects of FDA-Approved Opioids and Xtampza ER



* Data from NTX-blocked studies

5.3 Evaluation of Influence of Food in the Phase 3 Safety and Efficacy Study

The final way in which Collegium assessed the clinical relevance of the food effect of Xtampza ER was by evaluating clinical safety and efficacy with respect to food intake at dosing in the Phase 3 study (Study 08).

Detailed information regarding food intake at dosing was collected via subject electronic diaries. Subjects were instructed to record the meal type (i.e., no meal, snack, light meal, and heavy meal) in their e-diary. Subjects were provided examples of meals that fell into the 3 categories including a visual aid with example meal photographs; subjects were not instructed what to eat, but importantly, to assess meal size consistently throughout the study. Details of the overall study design and general efficacy results can be found in Section 7; general safety results are presented in Section 8.

5.3.1 Safety and Food Intake at Dosing

The relationship between safety and the food effect with Xtampza ER was assessed using two approaches: a pre-specified independently adjudicated food effect safety analysis and a series of post-hoc meal pattern analyses.

5.3.1.1 Food Effect Safety Analysis (Pre-Specified Analysis)

The first approach used an independent Adjudication Committee to determine whether SAEs and severe AEs with some level of Investigator-assessed causal relationship to study drug (termed

qualifying events) in the Phase 3 study were related to the food consumed at the time of the qualifying event. Consistent with guidance provided by the FDA in the 2011 Type A meeting, this approach was designed to determine whether any serious safety issues might be related to the food effect.

Ultimately, 3 AEs were deemed to be qualifying events per Investigator assessment. One qualifying event (anxiety) was in a subject on placebo, and the other 2 qualifying events (gastroesophageal reflux disease [GERD] and worsening erectile dysfunction) occurred in subjects on Xtampza ER. Both of these qualifying events were adjudicated to have no relationship among the event, study drug, and food consumed around the time of the event.

5.3.1.2 Meal Pattern Analysis Results (Post-Hoc Analysis)

The second approach assessed the possible relationship between AEs and food intake with Xtampza ER across the Phase 3 study (including the Titration Phase and Double-blind Maintenance Phase). This analysis tested the hypothesis that variation in food intake at the time of dosing may result in exposure differences that lead to AEs. For each AE in the study, the pattern of meals consumed on the day of, the day prior to (PM meal) and day of (AM meal), and the day prior to the AE were identified and analyzed to determine if a specific meal pattern was correlated with a higher incidence of AEs.

To define the meals associated with dosing the analysis utilized data collected in patient electronic diaries at the time of dosing, which included a qualitative description of the amount of food consumed with study drug (no meal, snack, light meal, or heavy meal). For the purpose of the analysis “no meal” and “snack” were combined into a “low” food intake category, and “light meal” and “heavy meal” were combined into a “high” food intake category.

Because the exact time of onset of an AE could not be determined (i.e., only the date of onset is known), the meal pattern analysis was conducted to encompass all dosing events that could reasonably have contributed to that AE. The temporal relationship between the dosing meal patterns analyzed and the AE are described in Table 13.

Tables located in Appendix 12.1 summarize the AE rates (per 100 person-days) for all AEs, AEs related to the study drug by the Investigator, and opioid-related specific AEs for each meal pattern. No consistent trends of clinically relevant differences in AE rates were observed across the various meal patterns (e.g., low-low, high-low) across the analyses as summarized in Table 13.

Table 13: Dosing Meal Pattern Analysis Summary

Temporal Relationship of Dosing Meals Relative to AE (Appendix Table)	AEs Analyzed	Conclusion
AM and PM day prior to AE (Appendix 12.1, Table 19)	All AEs	No association between food intake pattern and AEs
	Related AEs	
	Opioid-related AEs	
PM day prior and AM day of AE (Appendix 12.1, Table 20)	All AEs	No association between food intake pattern and AEs
	Related AEs	
	Opioid-related AEs	
AM and PM day of AE (Appendix 12.1, Table 21)	All AEs	No association between food intake pattern and AEs
	Related AEs	
	Opioid-related AEs	

5.3.2 Efficacy and Food Intake at Dosing

In addition to the safety assessments, an ad hoc efficacy analysis was conducted to determine whether specific meal patterns were associated with differences in subjects' 24-hour pain score across the Phase 3 study. A mixed model with 24-hour pain scores was estimated using 24-hour pain as the outcome, the meal pattern as the categorical predictor, and a random intercept for subject to account for the within-subject correlation. The results of this analysis showed that the pain scores reported in the course of a day were not significantly different by the type of meal pattern consumed on that day (Table 14).

Table 14: Summary of 24-Hour Pain Scores throughout the Phase 3 Study by Meal Pattern

Meal Pattern	Number of days with Meal Pattern	24-Hour Pain Score Mean (SE)
Low-Low	2127	4.0 (0.08)
Low-High	5410	4.1 (0.07)
High-Low	1738	4.1 (0.08)
High-High	11390	4.1 (0.07)

5.4 Conclusions Regarding Studies Characterizing Food Effect of Xtampza ER

Overall, the Xtampza ER clinical development program supports a “take with food” label. Based upon the totality of evidence, including PK studies conducted under clinically relevant conditions, comparisons to other marketed opioid products, and analysis of the Phase 3 study, the food effect with Xtampza ER is not expected to produce any clinically relevant consequences.

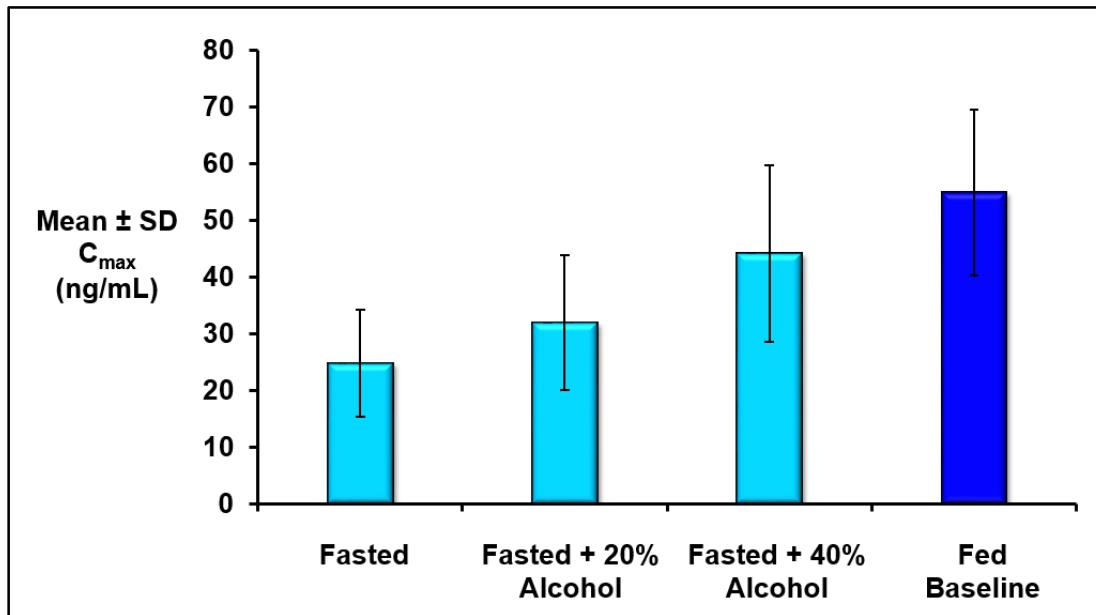
5.5 Effect of Alcohol on Bioavailability of Xtampza ER – Study 26

The impact of coingestion with alcohol and Xtampza ER was investigated in Study 26, an in vivo, open-label, randomized, 2-dose level, single-dose, NTX-blocked study in subjects designed based on guidance from FDA and based on in vitro alcohol interaction results. Based upon advice provided by FDA regarding the study design, alcohol challenge studies were conducted in the fasted state.

The study was conducted with two cohorts, which received either Xtampza ER at the highest (40 mg) or lowest (10 mg) dose strength under each of four conditions: (1) coingestion with 0% alcohol under HFHC conditions, (2) coingestion with 0% alcohol under fasted conditions, (3) coingestion with 20% alcohol under fasted conditions, and (4) coingestion with 40% alcohol under fasted conditions. The volume of water or water/alcohol consumed was 8 ounces in all cases. Each condition was separated by a washout period of at least 7 days between treatments. Because Xtampza ER is to be labeled to be taken with food, the PK profile observed under fed administration constitutes the appropriate comparator for evaluating the potential for dose dumping.

Administration of Xtampza ER (40 mg or 10 mg) with 20% and 40% alcohol under fasted conditions led to increased C_{max} values relative to fasted administration without alcohol. However, peak exposures with either 20% or 40% alcohol were lower than without alcohol following the fed baseline, which is the proposed labeled food instruction (Figure 30). Therefore, while alcohol increased exposure relative to fasted administration, similar to food, there is no evidence of “dose dumping” in the presence of alcohol.

Figure 30: Mean Peak Oxycodone Concentration with Xtampza ER 40 mg – Study 26



6 ALTERNATIVE METHODS OF DRUG ADMINISTRATION

Summary

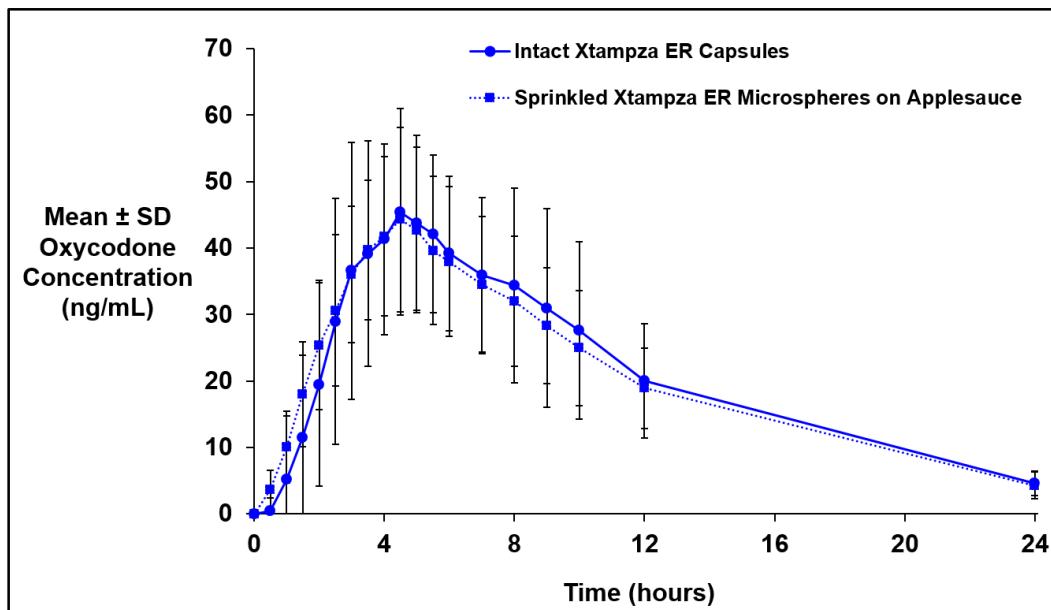
- Results from the Xtampza ER development program support the ability of the microsphere formulation to be sprinkled on food or directly into the mouth for patients who have difficulty or can't swallow pills as well as a dosing option for patients requiring a feeding tube.
- A single-dose NTX-blocked study demonstrated that the PK profile of Xtampza ER was bioequivalent when dosed intact orally as a capsule or when sprinkled onto applesauce in either fed or fasted conditions.
- Single dose studies conducted as part of the product's abuse-deterring evaluation demonstrated that chewing and crushing the microspheres did not compromise the extended-release plasma profile, supporting the safety of Xtampza ER for administration outside the capsules.
- In vitro dissolution studies demonstrated that the drug release characteristics and chemical stability of Xtampza ER were not altered after mixing microspheres with soft food and holding for up to 1 hour.
- Additional in vitro dissolution studies demonstrated that the drug release characteristics of Xtampza ER were maintained using 3 different feeding tubing lengths and diameters and 5 different delivery vehicles that are commonly used in clinical practice.

6.1 PK During Sprinkling onto Soft Food

Study 27 was an open-label, randomized, single-dose, 4-treatment, 4-period, NTX-blocked, crossover study of the relative oral PK of intact Xtampza ER compared to Xtampza ER sprinkled on applesauce. The treatment arms dosed Xtampza ER (40 mg) either intact as capsules or as microspheres sprinkled over applesauce under either fed (HFHC) or fasting conditions (40 mg).

The plasma profiles for the sprinkled and intact conditions were bioequivalent when comparing the intact and sprinkled dosing conditions for each of the fasted and HFHC meal conditions. Figure 31 shows the mean plasma oxycodone concentration over time for the sprinkled and intact conditions in the HFHC meal condition.

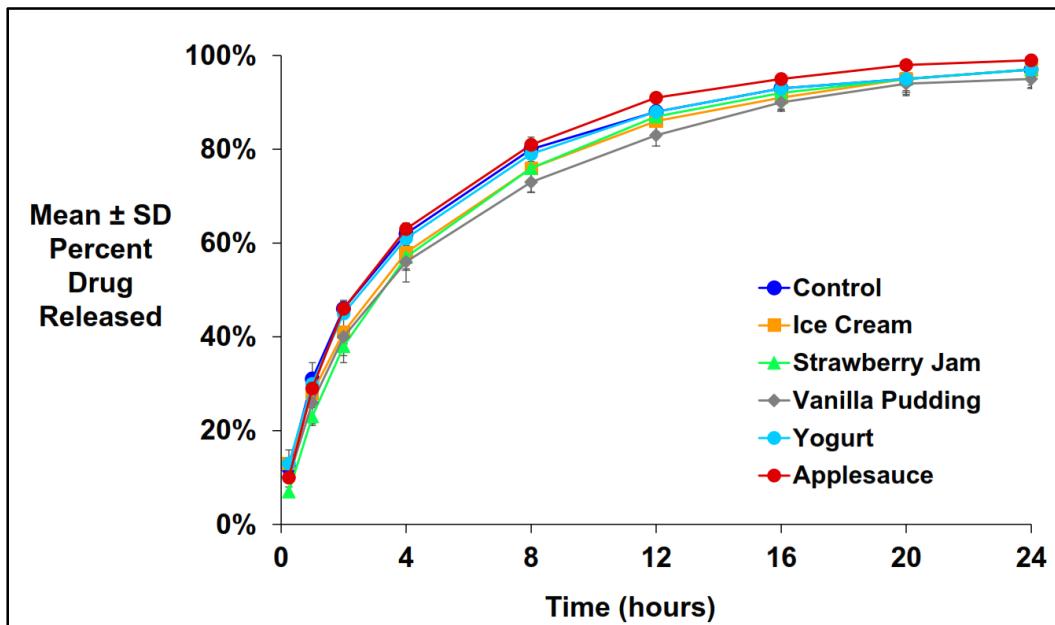
Figure 31: Oxycodone Concentration following Xtampza ER Administration Intact and Sprinkled onto Applesauce under Fed Conditions – Study 27



6.2 In Vitro Dissolution for Other Soft Foods

Multiple in vitro studies were conducted to determine the feasibility of administering Xtampza ER microspheres by sprinkling onto different soft foods (applesauce, vanilla pudding, strawberry jam, yogurt, and vanilla ice cream).

The drug release characteristics as measured by in vitro dissolution and chemical stability as measured by stability indicating assay of the capsule contents were not altered after mixing with any of the 5 soft foods and holding for up to 1 hour. Dissolution profiles for microspheres mixed with various soft foods are compared with control microspheres in Figure 32. The in vitro dissolution similarity factors (f_2) were >50 for all foods, meeting FDA's criterion for similarity.

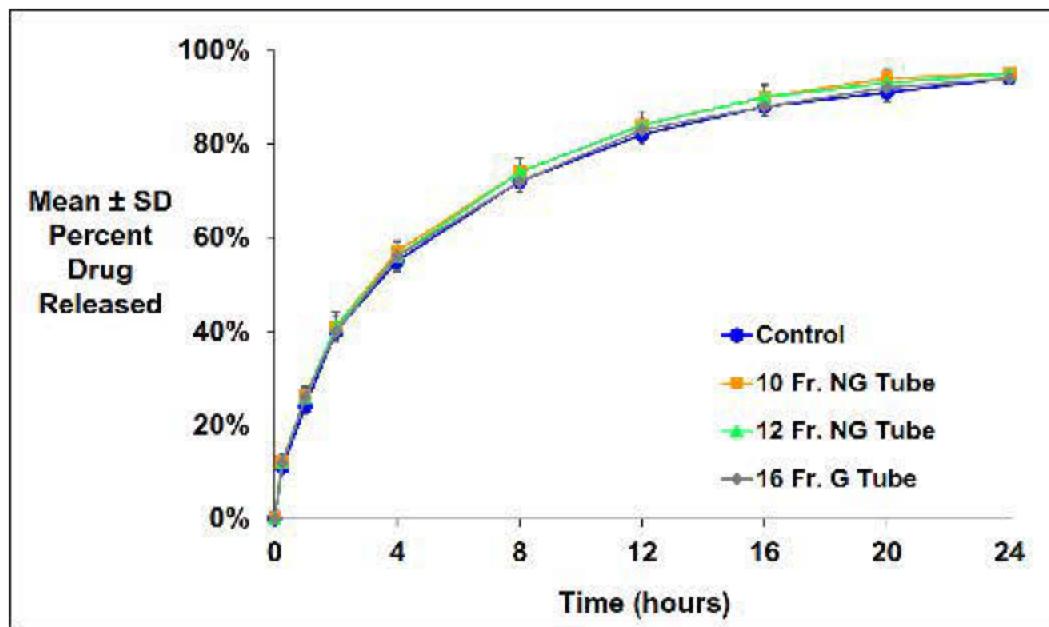
Figure 32: Xtampza ER Dissolution Profile Intact and Sprinkled on Various Soft Foods

6.3 In Vitro Studies of Dosing Via Nasogastric/Gastrostomy Tubes

A series of in vitro studies were conducted to determine the reliability of the administration of Xtampza ER microspheres using NG tubes (10 and 12 French) and a G tube (16 French), which represent 3 different feeding tubing lengths and diameters that are commonly used in clinical practice. The G tube selected for the studies is the smallest diameter used and is, therefore, representative of the most challenging scenario for passage of microspheres through available sizes of gastrostomy tubes. Various liquid vehicles used to flush microspheres down feeding tubes, including water, 2% milk, whole milk, and 2 commercial nutritional supplements (Jevity and Ensure).

Drug release characteristics, as measured by in vitro dissolution of the capsule contents, were not altered by passing through various feeding tubes with the aid of a variety of liquid vehicles. The f_2 values were >50 when comparing all tube/liquid vehicle combinations with the intact capsule reference curve, meeting FDA criteria for similarity. Figure 33 shows representative results from the in vitro study of feeding tubes using water as the liquid delivery vehicle, comparing the dissolution profiles with microspheres that were not passed through a tube.

Figure 33: Xtampza ER Dissolution Profile Intact and Passed through Feeding Tubes Using a Water Delivery Vehicle



7 CLINICAL EFFICACY IN PHASE 3 STUDY

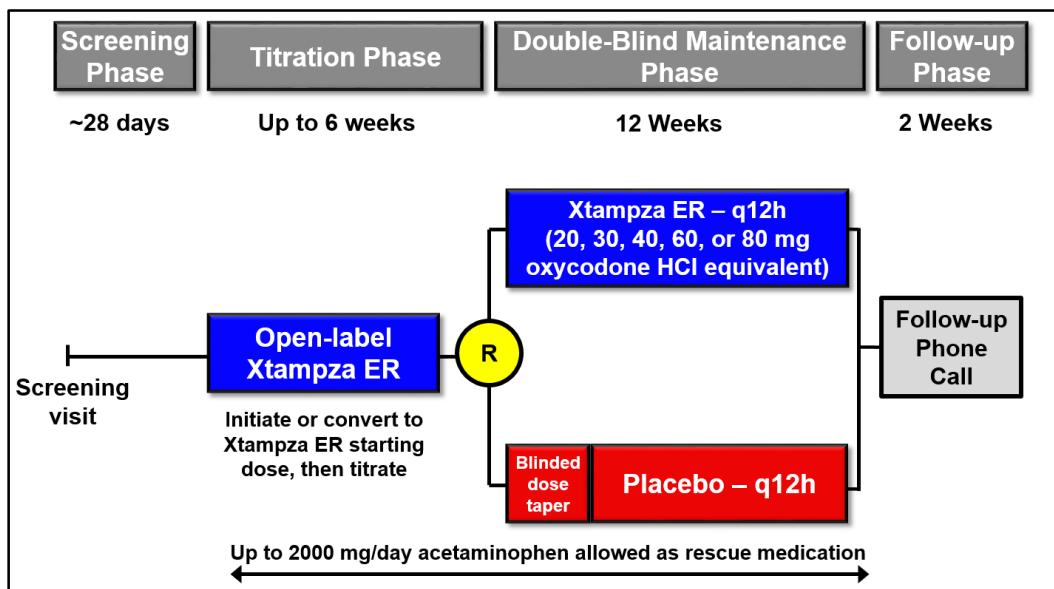
Summary

- Study 08 was a double-blind, placebo-controlled, enriched enrollment, randomized withdrawal (EERW) trial designed to demonstrate analgesic efficacy of Xtampza ER in subjects with moderate-to-severe chronic lower back pain. The study enrolled both opioid-experienced and opioid-naïve subjects.
- The study consisted of a Screening Phase (≤ 4 weeks), Titration Phase (≤ 6 weeks), Double-blind Maintenance Phase (12 weeks), and Safety Follow-up Phase (2 weeks).
- The primary efficacy endpoint was change in average pain intensity scores from Randomization Baseline to Week 12 as assessed by the Pain Intensity-Numerical Rating Scale (PI-NRS)
- During the Titration Phase in which subjects attempted to achieve a stable dose of Xtampza ER, mean pain scores were reduced from approximately a mean of 7 to a mean of 3 on the PI-NRS.
- The primary efficacy endpoint was met. Subjects in the Xtampza ER treatment group had statistically significantly better pain control than subjects in the placebo group ($P < 0.0001$). A treatment effect of 1.6 (95% CI: 1.0-2.1) is consistent with effect sizes reported in other trials of analgesics using the EERW study design.
- The significance of the primary endpoint was consistent across all sensitivity analyses performed.

7.1 Study Design

Study 08 was a double-blind, placebo-controlled, parallel-group, multicenter, enrollment-enriched, randomized withdrawal (EERW) trial. The trial was designed to demonstrate analgesic efficacy of Xtampza ER compared with placebo in subjects with moderate-to-severe CLBP. The EERW study design attributes are consistent with those used for other currently-approved opioid analgesics and are in accordance with recommendations from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) ([Dworkin et al., 2012](#)). The overall design and phases of Study 08 are shown in Figure 34.

Figure 34: Design of Phase 3 Study



R = Randomization Visit. q12h = every 12 hours.

7.1.1 Procedures and Assessments

7.1.1.1 Screening Phase

The Screening Phase of Study 08 lasted up to 4 weeks. Key inclusion criteria were that subjects had to have a history of CLBP for at least 6 months prior to screening requiring around-the-clock opioid analgesic, and subjects had to have an average 24-hour pain intensity score between 5 and 9 (inclusive) on the Pain Intensity-Numerical Rating Scale (PI-NRS) at the Screening Visit. The PI-NRS is an 11-point scale ranging from 0 (no pain) to 10 (worst possible pain).

7.1.1.2 Titration Phase

The Titration Phase of Study 08 lasted up to 6 weeks. The purpose of the Titration Phase was to titrate subjects, balancing analgesia with tolerability, to a stable, effective dose that would reduce their pain to ≤ 4 using the PI-NRS. Opioid-experienced subjects were converted from their current opioid medication(s) to Xtampza ER using a standard dose conversion table and dose conversion protocol that were included in the protocol; opioid-naïve subjects were started on the lowest dose of Xtampza ER (i.e., 10 mg every 12 hours [q12h]).

Xtampza ER was increased every 3 to 7 days up to a maximum daily dose of 160 mg (80 mg q12h) or until a stable dose was reached. A stable dose was defined as an unchanged dose of Xtampza ER for 7 days with no more than 2000 mg of rescue medication (acetaminophen) per day. By design, the intent of the titration schedule was to titrate slowly to a stable, effective dose in order to avoid exacerbation of pain flares or adverse events.

The principal criteria required to achieve a stable dose of study drug in order to be eligible for randomization included (1) an unchanged dose of Xtampza ER during the last 7 consecutive days prior to randomization; (2) a 24-hour PI-NRS score of ≤ 4 for 6 of the last 7 days prior to the Randomization Visit; (3) a reduction of ≥ 2 points in the average 24-hour PI-NRS score for ≥ 6 of the last 7 days prior to the Randomization Visit compared with the Screening Phase average pain score; and (4) up to 2000 mg acetaminophen per day as rescue medication.

Throughout the study, subjects were instructed to take their study drug with food and to record the meal type (i.e. no meal, snack, light meal, and heavy meal) and the timing of food intake and study drug intake in their electronic diary. No specific food type or amount was pre-specified, that is, subjects were not instructed what or how much to eat during the trial.

7.1.1.3 Double-Blind Maintenance Phase

The Double-blind Maintenance Phase lasted 12 weeks. Subjects who had achieved a stable dose of Xtampza ER in the Titration Phase were randomized to receive either Xtampza ER or matched placebo q12h. In order to minimize withdrawal symptoms, subjects randomized to placebo entered a blinded taper over the course of the first 20 days of the Double-blind Maintenance Phase.

At the end of the 12-week Double-blind Maintenance Phase or in the event of Early Discontinuation, subjects returned for end-of-study assessments and procedures. Subjects were switched to another opioid based on Investigator clinical practice; however, a suggested end-of-study switch instruction was provided to each Investigator.

7.1.1.4 Safety Phase

A follow-up safety phone call occurred 2 weeks after each subject completed or discontinued from the study to evaluate the safety of each subject.

7.1.2 Clinical Endpoints

7.1.2.1 Primary Efficacy Endpoint: Change in Average Pain Intensity Scores

The primary efficacy endpoint was change in the PI-NRS scores from Randomization Baseline (average of the daily PI-NRS scores from the 7 days prior to the Randomization Visit) to Week 12 (average of the daily PI-NRS scores for the final 7 days that the subject was on study).

Endpoint data were collected from subjects recording their average pain score over the past 24 hours each day at home in an electronic diary until the end of the study or early discontinuation. In addition, subjects recorded average pain score over the past 24 hours in the clinic at the Screening visit, Randomization visit, at end of study or early discontinuation, as well as at unscheduled visits. If rescue medication was used, the PI-NRS score recorded just prior to taking rescue medication was used to replace the daily 24-hour PI-NRS score for that day in the calculation of average weekly pain intensity scores.

7.1.2.2 Key Secondary Endpoints

Several secondary endpoints were pre-specified in the study. Three commonly evaluated secondary endpoints assessed in the Phase 3 study were:

- **Responder analyses:** the cumulative distribution of subjects with particular thresholds of improvement in pain intensity from Screening Baseline to Week 12 of the Double-blind Maintenance Period were calculated, with primary focus on the proportion of responders with $\geq 30\%$ and $\geq 50\%$ reductions in pain intensity
- **Time-to-exit:** the time-to-exit from the study for all causes from Randomization Baseline to Week 12 was calculated
- **Patient Global Impression of Change (PGIC):** the PGIC is a self-report, 7-point assessment of subjects' impressions of their change in activity limitations, symptoms, emotions, and overall quality of life as related to their painful condition and overall experience with the study treatment, which was completed at the end of the study or time of early discontinuation

7.1.3 Analysis Populations

Three primary analysis populations were defined for the assessment of efficacy and safety in the Phase 3 study:

- **ITT Population:** all subjects randomized with at least 1 post-randomization dose of study drug (Xtampza ER or placebo)
- **Safety Population:** all subjects who received at least 1 dose of study drug
- **Randomized Safety Population:** all subjects who were randomized and received at least 1 dose of study drug (Xtampza ER or placebo) during the Double-blind Maintenance Phase

7.2 Statistical Methodology

The primary statistical analysis for the primary efficacy endpoint was a 2-piece linear mixed model for the PI-NRS scores from Randomization Baseline through Week 12. A 2-piece linear model is a model with a linear response from Randomization Baseline to some post-randomization time (piece 1) and plateaus thereafter (piece 2). The intercepts and slopes are random effects with means that vary across mixture components; mixture components are the reason for discontinuation subgroups (e.g., completers, AEs, lack of efficacy).

A secondary analysis of the primary endpoint was conducted using the 24-hour daily pain score. For this alternative method, the weekly PI-NRS average scores were calculated based on 24-hour daily PI-NRS scores using the same rules as the primary endpoint for Week 12, and for Weeks 1 to 11, with the exception that pain scores at the time of rescue medication use for breakthrough pain were not used in computing the averages. The 2-piece linear mixed model was used as the statistical analysis method.

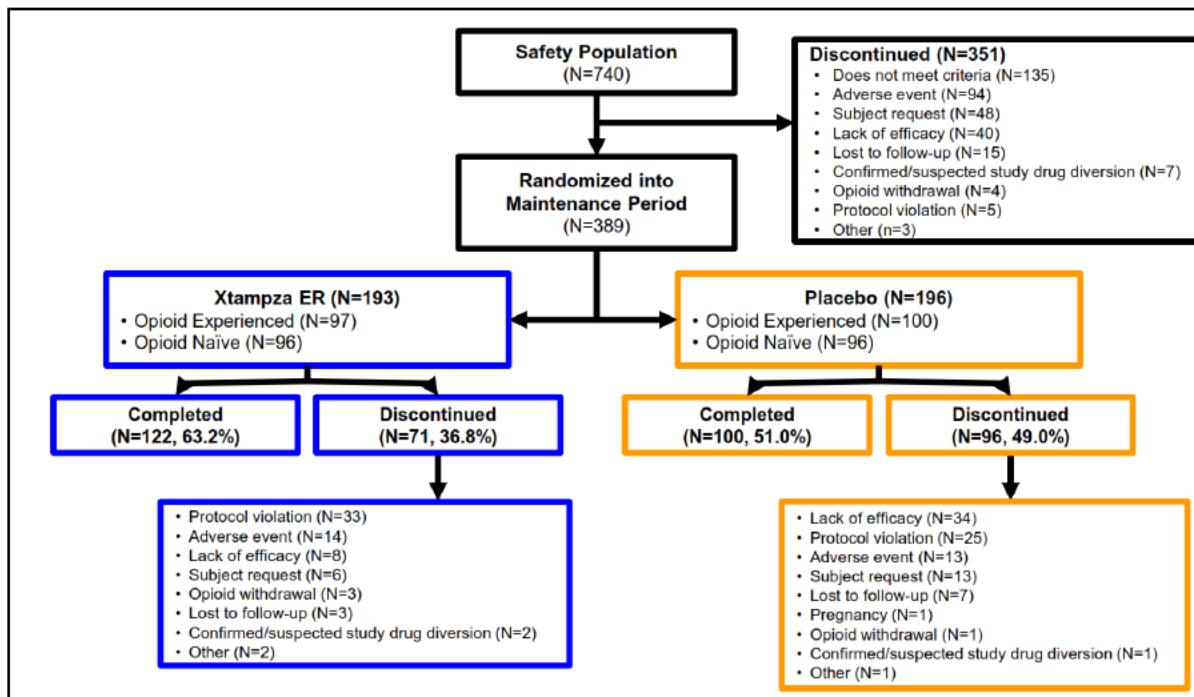
In addition to the secondary analysis with alternative parameterization of pain scores, several statistical methods were examined to test the robustness of the primary endpoint results across various assumptions. One sensitivity analysis for the primary endpoint was the change in average pain scores from Randomization Baseline to Week 12 for the ITT population, which was based on the 2-piece linear model for the placebo group and a linear model for the Xtampza ER group.

Another sensitivity analysis for the primary endpoint was conducted using a mixed model for repeated measures (MMRM) approach as an alternative likelihood approach. The MMRM model included a random effect for subject, visit, and treatment, including the interaction term between treatment and visit. The treatment difference was estimated using the change from Randomization Baseline to Week 12. Another sensitivity analysis included an imputation approach utilizing last observation carried forward (LOCF)/baseline observation carried forward (BOCF) in an analysis of covariance (ANCOVA).

7.3 Subject Disposition

Subject disposition is summarized in Figure 35. A total of 740 subjects entered Titration Phase and received at least 1 dose of Xtampza ER. During the Titration Phase, 351 subjects were discontinued. The rates of discontinuation were similar across patients receiving various doses. All subjects on 20 mg/day (lowest dose level) were discontinued due to failure to meet entrance criteria for randomization to the Double-blind Maintenance Phase of the study. The most common reasons for discontinuation during the Titration Phase included: failure to meet entrance criteria due to ineligibility for randomization (18.2%), adverse event (12.7%), subject request (6.5%), and lack of efficacy (5.4%).

Ultimately, 389 subjects (193 Xtampza ER, 196 placebo) were titrated to a stable dose and randomized and received at least 1 dose of Xtampza ER or placebo as part of the Double-blind Maintenance Phase (ITT Population). One hundred sixty-seven subjects discontinued in the Double-blind Maintenance Phase. The percentage of subjects who discontinued for each reason were similar between groups with the exception of discontinuation for lack of efficacy, which was higher in the placebo group.

Figure 35: Subject Disposition – Study 08


7.4 Demographics and Baseline Characteristics

Demographics/baseline characteristics were similar between the two treatment groups (Table 15).

Table 15: Demographic and Baseline Characteristics – Study 08 (ITT Population)

Characteristic	Xstampza ER (N = 193)	Placebo (N = 196)	Overall (N = 389)
Age, years – Mean ± SD	49.2 ± 13.3	49.9 ± 12.6	49.5 ± 12.9
Gender – n (%)			
Male	90 (46.6%)	93 (47.4%)	183 (47.0%)
Female	103 (53.4%)	103 (52.6%)	206 (53.0%)
Race – n (%)			
Caucasian/White	143 (74.1%)	133 (67.9%)	276 (71.0%)
Black or African American	39 (20.2%)	36 (18.4%)	75 (19.3%)
Asian	8 (4.1%)	23 (11.7%)	31 (8.0%)
American Indian or Alaska Native	2 (1.0%)	1 (0.5%)	3 (0.8%)
Native Hawaiian or Other Pacific Islander	0	1 (0.5%)	1 (0.3%)
Other	1 (0.5%)	2 (1.0%)	3 (0.8%)
Hispanic/Latino ethnicity – n (%)	16 (8.3%)	21 (10.7%)	37 (9.5%)
BMI, kg/m² – Mean ± SD	31.1 ± 7.1	31.2 ± 6.9	31.2 ± 7.0

BMI = body mass index; SD = standard deviation; ITT = intention-to-treat

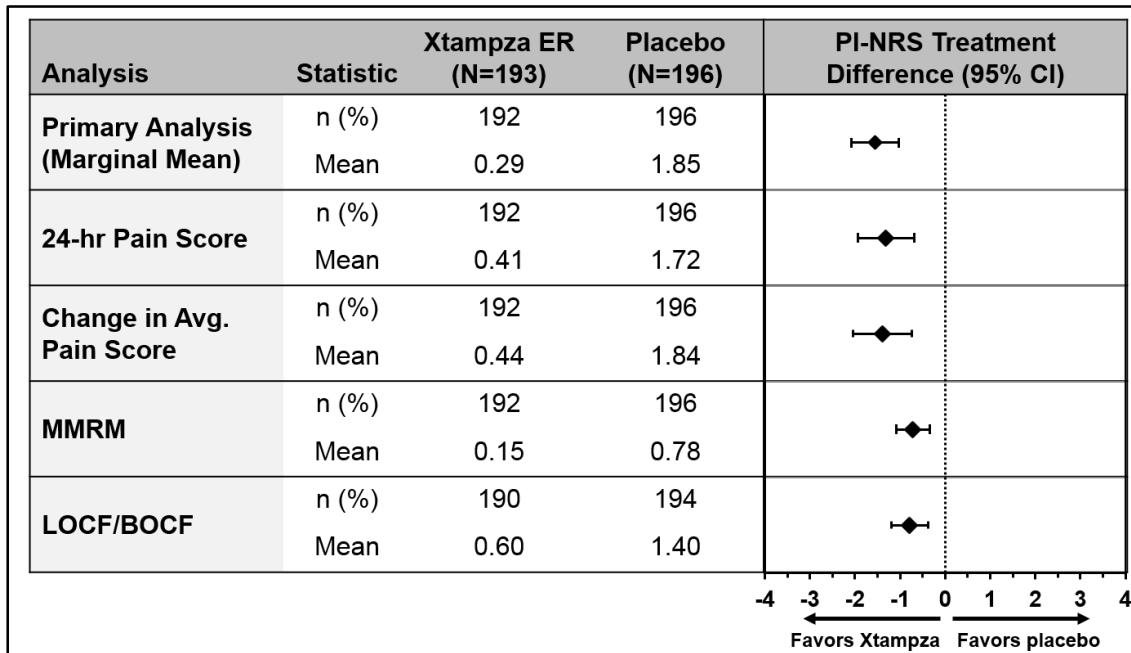
Prior to randomization, the percentages of subjects on Xtampza ER versus subjects on placebo on each stable dose per 12 hours (q12h) were, respectively: 20 mg (34.2% vs. 34.2%), 30 mg (22.3% vs. 21.4%), 40 mg (17.1% vs. 17.3%), 60 mg (13.0% vs 13.3%), and 80 mg (13.5% vs. 13.8%).

7.5 Primary Endpoint Results

The primary analysis of change in PI-NRS score from Randomization Baseline to Week 12 was statistically significant between the Xtampza ER and placebo groups, with significantly higher pain scores reported in the placebo group (treatment difference, 1.6; 95% CI, 1.0 to 2.1; P<0.0001).

Given the unique nature of the EERW design, it is important to understand the magnitude of the treatment difference in line with other clinically meaningful effects seen in similar EERW trials evaluating opioids in the treatment of chronic pain. The treatment effect observed in the Xtampza ER Phase 3 study is consistent with those observed in a systematic review of analgesics using the EERW trial design ([Katz, 2009](#)), which found a median treatment effect of 1.7. The analgesics included in the review included tramadol (for the treatment of CLBP and fibromyalgia), oxymorphone ER (for the treatment of CLBP), and adenosine (for the treatment of neuropathic pain).

Results of the secondary analysis of the primary endpoint as well as all sensitivity analyses for the primary endpoint, shown in Table 16, were also statistically significant (all P<0.001). The numeric results in Table 16 are the estimated change from Randomization Baseline to Week 12 for the various primary/sensitivity analyses. Positive scores represent an increase in pain from Randomization Baseline. The right hand of the Table shows a plot of the difference between treatments (calculated as Xtampza ER – placebo) with 95% CIs; negative values indicate that the placebo group had a greater increase in pain scores from Randomization Baseline to Week 12.

Table 16: Primary, Secondary, and Sensitivity Analyses of the Primary Endpoint

BOCF = baseline observation carried forward; ER = extended-release; CI = confidence interval; MMRM = mixed model with repeated measures. LOCF = last observation carried forward; MMRM = mixed model repeated measures. BOCF = baseline observation carried forward. Marginal mean = weighted average across mixture components (i.e., discontinuation subgroups) where the weights are the probabilities of component membership.

7.5.1 Consistency of Findings across Subgroups

The consistency of findings for the primary endpoint were examined in subgroups of the ITT population for age, sex, race, BMI, and prior opioid experience (i.e., opioid-experience and opioid-naïve). For each permutation except BMI <25 kg/m² and Non-Caucasians (which may be due to the small sample size [35 Xtampza ER and 39 placebo for BMI <25 kg/m²; 49 Xtampza ER and 63 placebo for Non-Caucasians], making inferential statistics indeterminate), the pooled analysis revealed a significant difference between the Xtampza ER and placebo groups with p-values ranging from <0.0001 to 0.046. The subgroup analysis for subjects 65 years and older did not converge because there was insufficient data for the statistical program to fit the model.

7.6 Key Secondary Endpoints

7.6.1 Responder Analysis for Pain Intensity at Week 12

In the ITT Population, a higher percentage of subjects in the Xtampza ER treatment group had a ≥30% improvement from Screening Baseline (95 subjects [49.2%]) compared with the placebo group (65 subjects [33.2%]), which was a statistically significant difference (P=0.001). More subjects in the Xtampza ER treatment group also had a ≥50% improvement from Screening Baseline (74 [38.3%] subjects) than subjects in the placebo group (48 subjects [24.5%]), which was also a statistically significant difference (p=0.003). In terms of the mean percentage

reduction in weekly PI-NRS scores from Screening Baseline to Week 12 of the Double-blind Maintenance Phase, subjects in the Xtampza ER treatment group had a 34% reduction compared to 25% for the placebo group, which was also statistically significant ($P=0.004$).

7.6.2 All-Cause Time-to-Exit from Study

Fewer subjects in the Xtampza ER treatment group (71 subjects [36.8%]) exited the study than in the placebo group (96 subjects [49.0%]), which was a statistically significant difference as assessed by the Kaplan-Meier method (log-rank $P=0.009$). As expected, the median time-to-exit was longer for subjects in the Xtampza ER treatment group (58 days) than for those in the placebo group (35 days).

7.6.3 Patient Global Impression of Change (PGIC)

In the ITT population, more subjects in the Xtampza ER treatment group reported improvement at Week 12 or at the final visit in their global impression of change than in the placebo group. At Week 12, 45.6% of subjects (n=88) in the Xtampza ER treatment group reported being “improved” or “very much improved” compared with 28.6% (n=56) of placebo subjects (Cochran-Mantel-Haenszel $P=0.004$). At the final visit, 66.8% of subjects (n=129) in the Xtampza ER treatment group reported being “improved” or “very much improved” compared with 46.4% (n=91) in the placebo group (Cochran-Mantel-Haenszel $P<0.0001$).

8 CLINICAL SAFETY IN PHASE 1 AND PHASE 3 STUDIES

Summary

- The safety profile in Phase 1 studies was generally consistent with that expected with OxyContin ADF.
- In the Phase 3 Study Titration Phase, 62% of the Safety Population reported an AE, which is commensurate with other, similar Phase 3 studies evaluating an opioid.
- In the Double-blind Maintenance Phase:
 - The percentage of subjects who reported an AE was higher in the Xtampza ER treatment group (65%) than the placebo group (49%), and the frequency of AEs were also higher on treatment, as expected.
 - The most common AEs reported in the Xtampza ER treatment group were nausea (11%), headache (6%), and constipation (5%).
 - The discontinuation rate for AEs was somewhat higher on treatment with approximately 8% in the Xtampza ER treatment group and 5% in the placebo group.
 - SAEs were balanced between treatment and placebo groups (1% in each group).
- Of the 65,613 doses of Xtampza ER administered across the study, there were no cases of SAEs/severe AEs associated with Xtampza ER (qualifying events).
- No new safety concerns were identified with administration of Xtampza ER for up to 4.5 months of treatment.

8.1 Summary of Safety in Phase 1

In the Xtampza ER Phase 1 development program, 448 subjects were exposed to at least 1 dose of Xtampza ER of whom 353 (79%) received NTX block. Forty-one of these subjects were exposed to multiple doses of Xtampza ER in Study 18. Given the limited exposure to Xtampza ER in Phase 1 studies and the confound of NTX block in most of these studies, the safety data from the Phase 3 Study are considered primary in the assessment of safety. No unexpected or unanticipated safety events occurred in the Phase 1 studies.

8.2 Ascertainment of Phase 3 Safety Data

In the Phase 3 Study, 740 subjects were exposed to 65,613 doses of Xtampza ER. The mean (SD) duration of treatment with Xtampza ER in the Titration Phase was 25.3 (12.8) days. The mean (SD) duration of treatment in the Double-blind Maintenance Phase with Xtampza ER was 64.7 (31.0) days and 55.9 (33.0) days with placebo.

In the Phase 3 study, AEs were collected from first dose of study drug through end of study or early discontinuation. SAEs were collected from the time of consent to 30 days following the last study drug dose. Routine safety assessments such as vital signs, clinical laboratory assessments

and urine drug screens were also performed. Opioid withdrawal was assessed at multiple time points during opioid tapering using the Clinical Opiate Withdrawal Scale (COWS) and the Subjective Opioid Withdrawal Scale (SOWS).

8.3 Safety in Phase 3 Study

8.3.1 Adverse Event Summary

In the Titration Phase, 462 subjects (62.4% of the Safety Population) reported 1197 AEs. There was one death on study, a sudden cardiac death that was not assessed as related to study drug by the Investigator, details of which can be found in Section 8.3.3. The most common AEs in Titration Phase were nausea (16.6%), headache (13.9%), and constipation (13.0%).

In the Double-blind Maintenance Phase, 125 subjects (64.8%) in the Xtampza ER treatment group and 95 subjects (48.5%) in the placebo group reported an AE. The rate of SAEs was 1.0% in both treatment groups, and the rate of discontinuation due to an AE was slightly higher in the Xtampza ER treatment group (7.8%) than the placebo group (5.1%). Table 17 provides an overview of AEs in the Double-blind Maintenance Phase.

Table 17: Overview of Adverse Events During the Double-blind Maintenance Phase – Study 08 (Randomized Safety Population)

Event Category	Xtampza ER (N = 193)		Placebo (N = 196)	
	n (%)	No. of Events (Events/PYR)	n (%)	No. of Events (Events/PYR)
Subjects with AEs	125 (64.8%)	293 (5.87)	95 (48.5%)	191 (4.15)
Subjects with SAEs	2 (1.0%)	2 (0.04)	2 (1.0%)	2 (0.04)
Subjects with Study Drug-associated SAEs/Severe AEs	0	0	1 (0.5%)	1 (0.02)
Subjects with AEs Leading to Study Drug Termination	15 (7.8%)	18 (0.36)	10 (5.1%)	11 (0.24)
Subjects with AEs Leading to Death	0	0	0	0

PYR = person-year

The most common AEs in the Xtampza ER treatment group during the Double-blind Maintenance Phase were nausea (10.9%), headache (6.2%), and constipation (5.2%). The most common AEs in the placebo group were headache (11.7%), nausea (4.6%), and upper respiratory tract infection (4.1%). Table 18 shows the percentages of subjects with all AEs that occurred at a rate of 3.0% or greater in the Xtampza ER treatment group in the Double-blind Maintenance Phase.

Table 18: Summary of Most Common Adverse Events with a Frequency $\geq 3\%$ in the Xtampza ER Group during Double-blind Maintenance Phase – Study 08 (Randomized Safety Population)

Preferred Term	n (%)	
	Xtampza ER (N=193)	Placebo (N=196)
Nausea	21 (10.9%)	9 (4.6%)
Headache	12 (6.2%)	23 (11.7%)
Constipation	10 (5.2%)	1 (0.5%)
Urinary Tract Infection	9 (4.7%)	2 (1.0%)
Diarrhea	8 (4.1%)	7 (3.6%)
Drug Withdrawal Syndrome	8 (4.1%)	3 (1.5%)
Fatigue	8 (4.1%)	2 (1.0%)
Vomiting	8 (4.1%)	3 (1.5%)
Nasopharyngitis	6 (3.1%)	4 (2.0%)
Upper Respiratory Tract Infection	6 (3.1%)	8 (4.1%)

8.3.2 Adverse Events Leading to Study Drug Termination

In the Titration Phase, 105 subjects (14.2%) had an AE that led to termination of study drug. The most common AEs that led to study drug termination were nausea (4.2%), vomiting (2.3%), somnolence (1.8%), dizziness (1.6%), and pruritus (1.2%).

In the Double-blind Maintenance Phase, 15 subjects (7.8%) in Xtampza ER treatment group and 10 (5.1%) in placebo group had an AE which led to early study drug termination. Most common preferred terms (PTs) were drug withdrawal syndrome (Xtampza ER, 1.6% [n=3] vs. placebo, 0.5% [n=1]), arthralgia (Xtampza ER, 1.0% [n=2] vs. placebo, 0% [n=0]), abdominal pain (0.5% [n=1] in both groups), vomiting (0.5% in both groups), and anxiety (0.5% in both groups).

8.3.3 Deaths

One death occurred in the Xtampza ER clinical program. A severe SAE of sudden cardiac death caused by cardiac arrest occurred during the Titration Phase of the Phase 3 study. The medical history of the subject included back pain and gross morbid obesity (weight 179.4 kg, BMI 53.9 kg/m²). This event was not considered related to the study drug by the Investigator.

8.3.4 Nonfatal Serious Adverse Events

Thirteen nonfatal SAEs occurred during the Phase 3 study. Two SAEs occurred prior to any study treatment. During the Titration Phase, 7 subjects (1.0% of Safety Population) reported 7 nonfatal SAEs, which all resolved without sequelae. During the Double-blind Maintenance

Phase, 4 subjects reported 4 SAEs (2 in the Xtampza ER treatment group, 2 in the placebo group), 3 of which resolved and 1 had an unknown outcome (subject was lost to follow-up).

9 POST-MARKETING RISK ASSESSMENT AND MANAGEMENT

Summary

- Collegium is committed to an extensive program to monitor misuse, abuse, addiction, and overdose.
- Xtampza ER has the class-wide REMS as part of its risk management strategy.
- Collegium is an observer company of the REMS Program Companies (RPC) will be an active member participant in the RPC and in the Opioid PMR Consortium.
- The drug safety and pharmacovigilance program will monitor for AEs, provide product information, implement recalls, manage complaints, and monitor for exceptional orders.
- Xtampza ER will have a robust abuse surveillance program encompassing multiple monitoring approaches, including monitoring of high prescribers, patients, physicians, pharmacies, distributors, and drug abuse forums/venues.
- Xtampza ER sales and marketing programs will be focused on experienced pain specialists and the sales force will be extensively trained to be compliant with all pertinent regulations including appropriate opioid prescribing guidelines.

Collegium is committed to an extensive program to monitor for safety issues including misuse, abuse, addiction, and overdose related to Xtampza ER. Xtampza ER will be a Schedule II drug under the Controlled Substances Act, which is the most restrictive schedule for a drug that has medical use, and will have appropriate class labeling for ER/LA opioids. In addition, it will be part of the class-wide Risk Evaluation and Mitigation Strategy (REMS) program and all Post-Marketing Requirement (PMR) studies mandated by the FDA. Collegium is an observer company in the REMS Program Companies (RPC) and will become a member company of RPC if Xtampza ER is approved by the Agency. In addition, Collegium is committed to joining the Opioid PMR Companies to actively contribute to the required PMR studies outlined by the Agency. Collegium will separately carry out (1) extensive surveillance for safety and diversion, (2) pharmacoepidemiology studies focused on misuse, abuse, addiction, and overdose, and (3) responsible sales and marketing of Xtampza ER.

As required by the FDA, Collegium will have a drug safety and pharmacovigilance program to monitor for AEs, product information, recalls, and complaints. This program will also monitor for exceptional orders in our supply chain to the level of the retail pharmacy, as exceptional orders may indicate inappropriate sales and diversion. Our manufacturing and supply chain will be monitored for compliance of all Drug Enforcement Administration (DEA) requirements. All pharmacovigilance personnel will be trained to assure understanding of the unique issues related to Class II opioids and to fully understand the Xtampza ER formulation in order to be well-equipped to service clinicians, other prescribing allied healthcare professions, and patients.

Because the federal surveillance systems (i.e., National Survey on Drug Use and Health, Monitoring the Future, National Forensic Laboratory Information System, and others) do not

collect specific brand-level data and the data are often a year old or older, we have contracted with vendors that can provide more timely brand-specific drug use data. We will conduct programs to monitor high prescribers to assess for inappropriate prescribing, patients who pay cash and use multiple prescribers and pharmacies, pharmacies that are dispensing exceptional amounts of Xtampza ER, and distributors that are filling exceptional orders. In addition, we will employ a multiple venue surveillance of prescription drug abuse monitoring/assessment program utilizing poison control center, drug diversion, opioid treatment, informant, and web data sources. In addition, Internet chat rooms will be monitored to see what comments are being made about the use and abuse of Xtampza ER and attempts to compromise our abuse-deterrent technology. Local print and electronic media will also be regularly monitored to determine if there are any reports of misuse, abuse, addiction, overdose, or diversion of Xtampza ER. Through this extensive monitoring system, Collegium will be able to determine how and to what extent Xtampza ER may be contributing to the misuse, abuse, addiction, diversion, and overdoses associated with ER prescription opioids. Regular reports on these findings will be filed with FDA.

The sales and marketing of Xtampza ER will be focused on experienced pain practitioners with a history of treating patients with chronic pain. This will enable monitoring to determine the extent of prescribing outside of the network of prescribers to whom we will be marketing the drug and the prescribing patterns of those prescribers within the network to whom we will be marketing. Our sales force will be extensively trained and periodically retrained to be compliant with all pertinent regulations. This training will include knowledge of appropriate prescribing as well as tools for the sales force to identify prescribers who may be using the drug outside of acceptable practice, and therefore, require more extensive prescriber education.

In addition to the package insert and standard Medication Guide, educational materials will be developed for patients, prescribers, and pharmacists consistent with the class-wide REMS. The patient education materials will focus on safe use and storage of their medication and the legal aspects of product diversion. The prescriber materials will address assessment of patients with chronic pain, how to monitor for possible abuse and diversion, problematic drug-drug interactions, and how to educate patients about safe use. The prescriber materials will also focus on the issue of dysphagia that often prevents patients from taking their opioid analgesic medication or leads to medication tampering to facilitate administration. Pharmacist education will include how to educate patients regarding appropriate use and storage, potential problematic drug interactions, and how to identify those who may be abusing or diverting their medication.

Collegium is aware of the problems associated with prescription drug abuse and will use the programs described above to help reduce this problem and to collect data that will inform necessary changes to the programs. While no formulation can solve these issues, Collegium aims to contribute to the public health goal of mitigating opioid abuse, first, by creating a product with strong abuse-deterrent properties, but also by implementing extensive educational programs for all stakeholders and collecting data that will help us understand the issues and apply strategies to reduce the problems.

10 BENEFIT-RISK ASSESSMENT

10.1 Class-wide Risks of Opioids

Chronic pain affects millions of adults in the US. Prescription opioid analgesics are an important component of modern pain management. In chronic pain conditions that are opioid responsive, a LA/ER opioid is often prescribed in conjunction with a short-acting opioid that is used to treat breakthrough pain.

While there remains a dire need for treatments for pain conditions, the risks associated with chronic opioid administration are well recognized, as evidenced by FDA's 2013 action to institute labeling changes to ER/LA opioid products including the clarification that they should be reserved for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. Like all opioid analgesics, Xtampza ER may increase the risk of serious adverse reactions such as respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, shock or neonatal opioid withdrawal syndrome. Prominent among the recognized risks of ER opioids is the potential for addiction, abuse, and misuse of these drug products; these risks have led to the development of abuse-deterrent formulations.

10.2 Benefits of the Novel Xtampza ER Microsphere Formulation

Collegium has developed Xtampza ER as an abuse-deterrent version of ER oxycodone with physical and chemical properties that make the formulation more difficult to manipulate for misuse and abuse. Xtampza ER contains pharmaceutically active microspheres delivered in a capsule for oral administration. While developed primarily to provide abuse-deterrent features, the microsphere-in-capsule design offers additional benefits relative to the currently marketed ER oxycodone tablet formulation (OxyContin ADF); the formulation enables patients to open the capsule and administer the contents directly into the mouth, onto soft food, or via an enteral tube, without compromising the ER properties of the product.

Throughout the clinical development program for Xtampza ER, efforts have been made to characterize the formulation properties with respect to key attributes of abuse deterrence, enhanced safety with respect to physical manipulation, and flexible dose administration. Specific benefits of the Xtampza ER formulation that have been established and discussed in this briefing document include the following:

- ***Established safety and efficacy in a 12-week study.*** In a 12-week EERW study in patients with CLBP, Xtampza ER was clinically and statistically superior to placebo in the subjects' change in average pain scores, the primary endpoint of the Phase 3 clinical study. This endpoint was achieved in a study design that used only acetaminophen rescue for breakthrough pain, and thus was not confounded by concurrent IR opioid treatment. No new safety concerns were noted with Xtampza ER administration beyond what has already been well documented for other oxycodone products. No meaningful differences in efficacy or safety were observed among subpopulations.

- **Abuse-deterrent properties with respect to the intranasal route of administration.** Results of in vitro studies have demonstrated that the microsphere formulation resists PSD when subjected to a variety of household tools and techniques. In 2 nasal PK studies, where the product was crushed with the most effective technique established in vitro, nasal administration of the crushed microspheres resulted in a relatively lower peak plasma concentration (C_{max}) and similar T_{max} when compared with intact oral administration. A HAP study demonstrated that crushed, nasally administered Xtampza ER had a statistically significantly lower Drug Liking peak effect (E_{max}) than crushed IR oxycodone administered intranasally. This finding for the primary endpoint of the study was supported by the analysis of secondary endpoints. Furthermore, the study showed that crushed IN Xtampza ER also had a statistically significantly lower Drug Liking E_{max} when compared with intact, oral Xtampza ER suggesting that the nasal route of abuse would not be preferred by abusers.
- **Abuse-deterrent properties with respect to manipulated, oral administration.** The effect of 2 types of product manipulation (crushing and chewing) on Xtampza ER PK was measured in 3 clinical studies where the capsule contents were either chewed or crushed (using the most effective technique identified in vitro) prior to administration. Collectively, the data from all 3 studies demonstrated that crushing or chewing the capsule contents prior to administration did not increase the maximum observed plasma concentration (C_{max}) or total exposure (AUC_{inf}) relative to dosing the product as intended (intact under fed conditions). A HAP study, conducted with chewed capsule contents, showed that the E_{max} for Drug Liking was significantly lower when comparing Xtampza ER chewed (fasted or fed) to IR oxycodone crushed solution fasted. Similarly, E_{max} for Drug Liking was significantly lower for both intact Xtampza ER fed and intact Xtampza ER fasted when compared with crushed IR oxycodone fasted. Consistent patterns of response to most PD endpoints and parameters by treatment indicate a decreased abuse potential profile for Xtampza ER relative to IR oxycodone.
- **Abuse-deterrent properties with respect to injection.** Xtampza ER resists preparation for IV injection when subjected to manipulations including extraction in small injectable volumes of water, attempting to force the melted capsule contents through a hypodermic needle, and attempting to directly inject the microspheres suspended in water through a needle.
- **Safety benefits related to inadvertent product manipulation by patients.** The data from 3 PK studies demonstrated that crushing or chewing the capsule contents prior to administration did not increase the maximum observed plasma concentration (C_{max}) or total exposure (AUC_{inf}) relative to dosing the product as intended (intact under fed conditions). The observed C_{max} values for manipulated Xtampza ER treatments following oral administration in these studies were significantly lower than IR oxycodone treatments and the time of the maximum measured plasma concentration (T_{max}) values significantly longer, consistent with Xtampza ER retaining its ER nature and an absence of “dose dumping”. In contrast, the C_{max} observed with manipulated OxyContin ADF was bioequivalent to crushed IR oxycodone tablets with a similar T_{max} (Study 25); a published study also demonstrated that chewing OxyContin ADF tablets also produces an IR PK

profile (Harris, 2012). Based on the ability to convert OxyContin ADF from the intact ER formulation to an IR formulation upon tampering, Xtampza ER potentially poses a lower safety risk relative to OxyContin ADF; this risk is potentially further lowered by the fact that Xtampza ER is available in doses only up to 40 mg, whereas OxyContin ADF tablets are available at doses of up to 80 mg.

- **Flexible dose administration options.** This formulation offers an important advantage over ER opioid products that must be taken intact, in that the free-flowing microspheres that compose the Xtampza ER formulation may be administered as a sprinkle onto soft foods, directly into the mouth, or through a NG or G feeding tube without effect on the drug's dissolution or PK profile. This is particularly important given postmarketing reports of difficulties with OxyContin ADF (including choking, gagging, regurgitation, and tablets stuck in the throat), necessitating label instructions to consider use of an alternative analgesic in patients who have difficulty swallowing. Xtampza ER, therefore, offers a solution to a critical unmet medical need for individuals with aversion to or difficulty swallowing intact tablets, for whom there is currently no ER oxycodone option for pain control.

10.3 Food Effect of Xtampza ER

Extensive efforts were undertaken to characterize both the PK and clinical implications of the food effect observed with Xtampza ER. The product food effect observed in single-dose studies conducted in NTX-blocked subjects was further studied in order to place it into the appropriate context of clinical use, that is, in chronic dosing of subjects for the treatment of pain and without NTX block. These efforts characterized the following:

- the effect of differing meal composition on PK;
- the food effect in a steady state context relative to OxyContin ADF;
- the effect of food in subjects without concomitant administration of NTX; and
- the possibility of association of AEs or efficacy in the Phase 3 clinical study with food intake

In summary, the following conclusions have been derived from these studies:

- In a single-dose, NTX-blocked study, bioavailability of Xtampza ER was similar to OxyContin ADF when dosed with any amount of food, but was lower under fasted conditions. Xtampza ER will, therefore, be labeled “take with food”.
- Under steady-state conditions, taking Xtampza ER in the fasted state—even at every other meal—only modestly affects drug exposure, and still provides a 24-hour PK profile that is bioequivalent to OxyContin ADF dosed under the same alternating fed/fasted conditions.
- PK data from Study 24, which found bioequivalent exposure (AUC) in the fasted and fed conditions without co-administration of NTX, coupled with the reduced magnitude of the food effect from the PK data from Study 18 suggest that the magnitude of the food effect

will be smaller under actual clinical-use conditions. A review of published data showed that the food effect of Xtampza ER without NTX block is within the range of other approved opioid products.

- No influence of food consumption on the safety and efficacy profile of Xtampza ER was identified in the Phase 3 safety and efficacy study. In spite of the breadth of study drug exposure in the Phase 3 study (>65,000 doses of Xtampza ER), no SAEs or severe AEs showed a relationship with food. The Phase 3 data did not identify any prospective food effect attributable to Xtampza ER; no SAEs/severe AEs were associated with Xtampza ER; the analyses of dosing meal patterns showed no association of food with exacerbation of AEs; and there was no correlation between the amount of food consumed and daily average pain scores.

Thus, the preponderance of evidence supports the conclusion that under real-world conditions, the effect of food intake variations should be minimal and Xtampza ER should provide consistent, safe, and therapeutic oxycodone exposures day after day for patients seeking reliable, sustained pain control. However, because the observed food effect (comparing fasted administration with fed meal administration) is larger than for the listed drug OxyContin ADF, Collegium is proposing that the label include the instruction to take Xtampza ER with food in order to reduce the potential for reduced plasma exposure based on fasted administration.

10.4 Overall Conclusion

In summary, the data presented in this document show that Xtampza ER, when administered with food, produces an oxycodone plasma concentration-time profile similar to that of OxyContin ADF, retains the ER properties of the intact capsule after physical manipulation such as crushing or chewing (creating a margin of safety in the event of inadvertent manipulation), has a reduced potential for abuse by the oral, nasal, and IV routes compared with IR oxycodone, and addresses an unmet medical need for patients with difficulty swallowing intact tablet/capsule formulations. Data from the pivotal safety and efficacy Phase 3 demonstrate that Xtampza ER is safe and effective for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. It is recognized that abuse-deterrent formulations, along with education, awareness, and proper prescribing practices, all play a role in reducing both the health and economic burdens of the prescription opioid abuse epidemic. Therefore, once marketed, clinically appropriate prescribing and patient use practices will be encouraged by means of implementing the Risk Evaluation and Mitigation Strategy (REMS) for Xtampza ER, which adheres to the class-wide ER/LA REMS recommendations from FDA.

Overall, Xtampza ER represents an important new pain management tool, with a meaningfully reduced potential for abuse compared with other marketed opioid products, for individuals requiring day-to-day control of chronic pain.

11 REFERENCE LIST

1. American Academy of Pain Medicine. AAPM Facts and Figures on Pain. 2013. Chicago, IL. Available at: http://www.painmed.org/patientcenter/facts_on_pain.aspx. Accessed April 11, 2013.
2. Argoff CE, Kopecky EA. Patients with chronic pain and dysphagia (CPD): unmet medical needs and pharmacologic treatment options. *Curr Med Res Opin* 2014;30(12): 2543-2559. doi: 10.1185/03007995.2014.967388
3. Bashaw ED, Kaiko RF, Grandy RP, et al. Relative bioavailability of controlled-release oral morphine sulfate during naltrexone blockade. *Int J Clin Pharmacol Ther* 1995;33:524-9.
4. Butler SF, Black RA. Relative abuse of deterrent formulations via alternative oral routes. Manuscript in preparation. Inflexxion, Inc. Newton, MA 02464.
5. Butler SF, Budman SH, Licari A, et al. National addictions vigilance intervention and prevention program (NAVIPPRO): a real-time, product-specific, public health surveillance system for monitoring prescription drug abuse. *Pharmacoepidemiol Drug Saf* 2008;17(12):1142-54.
6. Butler SF, Cassidy TA, Chilcoat H, et al. Abuse rates and routes of administration of reformulated extended-release oxycodone: initial findings from a sentinel surveillance sample of individuals assessed for substance abuse treatment. *J Pain* 2013;14:351-8.
7. Center for Drug Evaluation and Research (CDER). Draft Guidance for Industry: Abuse-Deterrent Opioids —Evaluation and Labeling. Rockville, MD: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research; 2013.
8. Center for Drug Evaluation and Research (CDER). Guidance for Industry: Abuse-Deterrent Opioids —Evaluation and Labeling. Rockville, MD: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research; 2015a.
9. Center for Drug Evaluation and Research (CDER). Guidance for Industry: Naming of Drug Products Containing Salt Drug Substances. Rockville, MD: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research; 2015b.
10. Center for Drug Evaluation and Research (CDER). Guidance for Industry: Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules. Rockville, MD: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research 2015c.
11. Dworkin RH, Turk DC, Peirce-Sandner S, et al. Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. *Pain* 2012;153:1148-58.
12. Harris S. Effects of various tampering methods on exposure to oxycodone in healthy subjects. Poster presented at: 74th Annual Scientific Meeting of the College on Problems of Drug Dependence (Poster #78). 2012.

13. Huizer H. Analytical studies on illicit heroin. V. Efficacy of volatilization during heroin smoking. *Pharm Weekbl Sci* 1987;9:203-11.
14. Johannes CB, Le TK, Zhou X, et al. The prevalence of chronic pain in United States adults: results of an Internet-based survey. *J Pain* 2010;11:1230-9.
15. Katz N. Enriched enrollment randomized withdrawal trial designs of analgesics: focus on methodology. *Clin J Pain* 2009;25:797-807.
16. Kelly J, Wright D, Wood J. Medicine administration errors in patients with dysphagia in secondary care: a multi-centre observational study. *J Adv Nurs* 2011;67:2615-27.
17. Lange B, Kuperwasser B, Okamoto A, et al. Efficacy and safety of tapentadol prolonged release for chronic osteoarthritis pain and low back pain. *Adv Ther* 2010;27:381-99.
18. Maxwell JC. The prescription drug epidemic in the United States: a perfect storm. *Drug Alcohol Rev* 2011;30:264-70.
19. Meyer RJ, Hussain AS. Awareness topic: mitigating the risks of ethanol induced dose dumping from oral sustained/controlled release dosage forms. FDA Advisory Committee for Pharmaceutical Science (ACPS) Meeting. 2005.
20. Moorman-Li R, Motycka CA, Inge LD, et al. A review of abuse-deterrent opioids for chronic nonmalignant pain. *P T* 2012;37(7):412-8.
21. New Drug Application No. 021610. Opana ER (oxymorphone hydrochloride [tablet, extended release; oral]). Original Approval June 22, 2006. Endo Pharmaceuticals.
22. New Drug Application No. 021611. Opana (oxymorphone hydrochloride [tablet; oral]). Original Approval June 22, 2006. Endo Pharmaceuticals.
23. New Drug Application No. 022272. OxyContin (oxycodone hydrochloride [tablet, extended release; oral]). Original Approval April 5, 2010. Purdue Pharmaceuticals L.P.
24. New Drug Application No. 020553. OxyContin (oxycodone hydrochloride [tablet, extended release; oral]). Original Approval December 12, 1995. Purdue Pharmaceuticals L.P.
25. Parsells KJ, Cook SF, Kaufman DW, et al. Prevalence and characteristics of opioid use in the US adult population. *Pain* 2008;507-13.
26. Pergolizzi J, Boger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract* 2008;8:287-313.
27. Pergolizzi JV, Gharibo CG, Gudin JA, Nalamachu SR. Development of federally mandated risk evaluation and mitigation strategies (REMS) for transmucosal immediate-release fentanyl products. *Pain Pract* 2013;13:259-63.
28. Pergolizzi JV, Taylor R, Nalamachu S, et al. Challenges of treating patients with chronic pain with dysphagia (CPD): physician and patient perspectives. *Curr Med Res Opin* 2014;30(2):191-202.

29. Purdue Pharma L.P. Prescribing Information for OXYCONTIN – oxycodone hydrochloride tablet, film coated, extended release. Available at:
<http://www.purduepharma.com/oxycontinpi>. Accessed August 1, 2015.
30. Sathyan G, Xu E, Thipphawong J, Gupta SK. Pharmacokinetic profile of a 24-hour controlled-release OROS formulation of hydromorphone in the presence and absence of food. *BMC Clin Pharmacol* 2007;7:2.
31. Substance Abuse and Mental Health Services Administration, Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-48, HHS Publication No. (SMA) 14-4863. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2014.
32. Warner M, Hedegaard H, Chen L. Trends in drug-poisoning deaths involving opioid analgesics and heroin: United States, 1999-2012. 2014. Available at:
http://www.cdc.gov/nchs/data/hestat/drug_poisoning/drug_poisoning.htm. Accessed December 19, 2014.

12 APPENDIX

12.1 Meal Pattern Safety Analysis Tables

Table 19: Summary of AE Rates by Prior Day Meal Pattern

	N events (rate per 100 person-days)			
	Low-Low (N=2633)	Low-High (N=6826)	High-Low (N=2214)	High-High (N=14,466)
All AEs	99 (3.8)	253 (3.7)	67 (3.0)	417 (2.9)
Mild	57 (2.2)	164 (2.4)	48 (2.2)	283 (2.0)
Moderate	42 (1.6)	87 (1.3)	19 (0.9)	132 (0.9)
Severe	0 (0.0)	2 (<0.1)	0 (0.0)	2 (<0.1)
Related AEs	62 (2.4)	153 (2.2)	36 (1.6)	247 (1.7)
Mild	36 (1.4)	102 (1.5)	25 (1.1)	180 (1.2)
Moderate	26 (1.0)	51 (0.7)	11 (0.5)	67 (0.5)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Opioid-associated AEs ¹	36 (1.4)	78 (1.1)	19 (0.9)	119 (0.8)
Mild	26 (1.0)	50 (0.7)	10 (0.5)	86 (0.6)
Moderate	10 (0.4)	28 (0.4)	9 (0.4)	32 (0.2)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)

Note: N = Number of dosing days. Low = “no meal” or “snack”. High = “light meal” or “heavy meal”.

¹ Opioid-associated AEs included those with the following coded terms: Nausea, Vomiting, Pruritus, Somnolence, Sedation, Hyperhidrosis, Dizziness, Confusional State, and Cognitive Disorder.

Table 20: Summary of AE Rates by Prior PM Meal and Current AM Meal Pattern

	N events (rate per 100 person-days)			
	Low-Low (N=2662)	Low-High (N=2249)	High-Low (N=6777)	High-High (N=14,521)
All AEs	94 (3.5)	79 (3.5)	252 (3.7)	431 (3.0)
Mild	56 (2.1)	55 (2.4)	162 (2.4)	298 (2.1)
Moderate	38 (1.4)	24 (1.1)	89 (1.3)	132 (0.9)
Severe	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Related AEs	50 (1.9)	56 (2.5)	154 (2.3)	275 (1.9)
Mild	28 (1.1)	39 (1.7)	105 (1.5)	199 (1.4)
Moderate	22 (0.8)	17 (0.8)	49 (0.7)	76 (0.5)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Opioid-associated AEs ¹	29 (1.1)	29 (1.3)	73 (1.1)	138 (1.0)
Mild	20 (0.8)	20 (0.9)	47 (0.7)	105 (0.7)
Moderate	9 (0.3)	9 (0.4)	26 (0.4)	33 (0.2)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: N = Number of dosing days. Low = “no meal” or “snack”. High = “light meal” or “heavy meal”.

¹ Opioid-associated AEs included those with the following coded terms: Nausea, Vomiting, Pruritus, Somnolence, Sedation, Hyperhidrosis, Dizziness, Confusional State, and Cognitive Disorder.

Table 21: Summary of AE Rates by Current Day Meal Pattern

	N events (rate per 100 person-days)			
	Low-Low (N=2650)	Low-High (N=6875)	High-Low (N=2235)	High-High (N=14,565)
All AEs	106 (4.0)	243 (3.5)	77 (3.4)	424 (2.9)
Mild	61 (2.3)	164 (2.4)	55 (2.5)	292 (2.0)
Moderate	45 (1.7)	78 (1.1)	21 (0.9)	131 (0.9)
Severe	0 (0.0)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Related AEs	65 (2.5)	147 (2.1)	54 (2.4)	270 (1.9)
Mild	36 (1.4)	104 (1.5)	41 (1.8)	195 (1.3)
Moderate	29 (1.1)	43 (0.6)	13 (0.6)	75 (0.5)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Opioid-associated AEs ¹	31 (1.2)	72 (1.0)	28 (1.3)	135 (0.9)
Mild	21 (0.8)	55 (0.8)	20 (0.9)	104 (0.7)
Moderate	10 (0.4)	17 (0.2)	8 (0.4)	31 (0.2)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: N = Number of dosing days. Low = “no meal” or “snack”. High = “light meal” or “heavy meal”.

¹ Opioid-associated AEs included those with the following coded terms: Nausea, Vomiting, Pruritus, Somnolence, Sedation, Hyperhidrosis, Dizziness, Confusional State, and Cognitive Disorder.