CLINICAL PROTOCOL

AN OPEN-LABEL STUDY TO EVALUATE THE PHARMACOKINETICS AND SAFETY OF ALO-02 (OXYCODONE HYDROCHLORIDE AND NALTREXONE HYDROCHLORIDE) EXTENDED-RELEASE CAPSULES IN CHILDREN AND ADOLESCENTS 7-17 YEARS OF AGE WHO REQUIRE OPIOID ANALGESIA

Compound:	ALO-02 (PF-06412527)
Compound Name:	oxycodone hydrochloride and naltrexone hydrochloride extended-release capsules
United States (US) Investigational New Drug (IND) Number:	107,037
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Phase:	4

[redacted]

[redacted]

Document History

Document	Version Date	Summary of Changes
Amendment 1	06 July 2016	A substantial change will be preceded by (SC). All other changes are administrative changes as required by the latest protocol template. **SC Table 3 ALO-02 Total Daily Dose and Dosing Schedule** now has lower doses of 3 mg, 5 mg and 15 mg of oxycodone with naltrexone. **Appendix 6** was deleted because it was redundant Columbia-Suicide Rating Scale (C-SSRS) Baseline Age 12-17 years is Appendix 4. **Visit 5** was clarified from Visit 5/Early Termination to Visit 5/Early Termination/End-of-Study Visit. **Visit 6** was clarified from Follow-Up/End-of-Study to Visit 6/Follow-Up/Post-Treatment Period. **Visit 6** was clarified that it can be an office visit or a telephone call at the discretion of the investigator. **Diary** was changed from eDiary to Diary since an electronic diary is not being used in this study. **Schedule of Activities** telephone calls added a call at Visit 2. Added footnote 19 which states, "The Follow UP? Post Treatment Visit, this may be done over the telephone at the Investigator's discretion." Added Footnote 20 which states, "The investigator or his/her designee will discuss with the subject/caregiver the need to use highly effective contraception consistenly and correctly according to the Schedule of Activities and document such conversations in the subject's chart." Added Contraception Check to remind to check with the subject/caregiver. Added Emergency Card so the site is aware when to give the emergency card to the subject. **Appendix 2** added dosing chart for drug conversion guidelines at the dose level for ease of conversion at the sites and to be consistent with the Embeda protocol.
Original protocol	02 April 2015	Not Applicable (N/A)

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PROTOCOL SUMMARY

Background and Rationale:

ALO-02 (PF-06412527) is a combination opioid agonist/opioid antagonist product indicated 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.

ALO-02 capsules consist of controlled-release pellets containing oxycodone hydrochloride (HCl) and naltrexone HCl. The pellet formulation is designed to release oxycodone in an extended-release (ER) manner over time while retaining naltrexone HCl in the inner core unless the inner core is disrupted. Upon crushing or chewing the pellets, naltrexone is released along with the oxycodone, thereby, attenuating the liking and euphoric effects of the opioid. Naltrexone HCl is formulated in a 12% (w/w) ratio in combination with oxycodone HCl across all dosage strengths. ALO-02 was developed with the goal of decreasing misuse, abuse, and diversion of opioids; an increasing public health problem among many age groups, including adolescents.

One of the major challenges facing clinicians who wish to prescribe pain medications to children and adolescents is the paucity of information in the pediatric population about the proper choice of pain medication, dosage guidelines, and expectations with regard to efficacy and untoward effects. Efforts to address this challenge include the Best Pharmaceuticals for Children Act (BPCA)[1] and the Pediatric Research Equity Act (PREA).[2] The study is being conducted as a Phase 4 post-marketing requirement to the Food and Drug Administration (FDA) consistent with ICH E11 guidelines for "Clinical Investigation of Medicinal Products in the Pediatric Population".

The proposed study is intended to characterize the pharmacokinetics (PK) of ALO-02 and evaluate the safety of ALO-02 in children and adolescents 7 to 17 years of age who require opioid analgesia for moderate-to-severe pain.

Objectives:

Primary

- To characterize the PK of oxycodone in children and adolescents 7 to 17 years of age treated with ALO-02.
- To evaluate the safety of ALO-02 in children and adolescents 7 to 17 years of age.

Secondary

- To determine the systemic exposures of naltrexone and 6-β-naltrexol in children and adolescents 7 to 17 years of age treated with ALO-02.

Endpoints:

Primary

- *Pharmacokinetics:* estimates of oxycodone average steady-state concentration ($C_{ss,av}$) and apparent oral clearance (CL/F).

- *Safety:* incidence, intensity, relationship, and seriousness of adverse events (including symptoms of opioid withdrawal or overdose).

Secondary

- *Pharmacokinetics:* apparent volume of distribution (V_z/F) of oxycodone, data permitting; and systemic exposure levels of the metabolites of oxycodone (oxymorphone and noroxycodone), naltrexone, and 6-β-naltrexol.

- *Safety:* changes in vital signs (blood pressure, heart rate, respiratory rate), clinical chemistry, and hematology laboratory values.

Other

- *Analgesic effect:* pain intensity scores (actual and % change from baseline) and rescue medication or additional analgesic medication use over time.

- *Pharmacokinetics:* graphical representations and regression analyses may be used to characterize the dose-exposure relationships for oxycodone, naltrexone, and 6-β-naltrexol.

Study Design:

This is a multicenter, open-label, single-arm study designed to characterize the PK and evaluate the safety of ALO-02 in opioid experienced children and adolescents with moderate-to-severe pain. The study will enroll approximately 140 children and adolescents to achieve at least 100 subjects exposed to at least 2 weeks of treatment with ALO-02 in the Maintenance Phase. Plasma samples will be collected during the Maintenance Phase under steady-state conditions to characterize the pharmacokinetics of oxycodone and determine the systemic exposures of oxymorphone, noroxycodone, naltrexone, and 6-β-naltrexol.

The study consists of 4 study periods including occurring over a period of up to 9 weeks:

- Screening Period (Visit 1) lasting up to 2 weeks.

- Treatment Period (Visits 2-5) lasting up to 6-8 weeks.

- Follow-Up/Post-Treatment Period (Visit 6) lasting 1 week.

All subjects will be treated with ALO-02 capsules for oral use for up to 8 weeks in this single-arm, open-label study. Subjects must be taking opioids prior to entry into the study. Initial ALO-02 dose will be determined by the subject's pre-study opioid treatment prior to the Conversion/Titration Period. The Treatment Period duration is 6 to 8 weeks and consists of two phases of variable lengths depending on when a subject achieves a stable dose of ALO-02 and how long opioid analgesia is required.

Assessments:

Safety Assessments

After signing the consent/assent and before admission to the study, subjects will undergo a physical examination and testing procedures/measurements including 12-lead electrocardiogram (ECG), blood pressure, heart rate, and clinical and laboratory testing. During the study, the investigator will closely monitor adverse events including, but not limited to, opioid overdose and/or signs and symptoms of opioid withdrawal.

Pharmacokinetic Assessments

Once a subject has achieved a stable dose of ALO-02, two 6 mL (2×6 mL) blood samples will be collected on the same day at least 2 hours apart for the purpose of quantifying concentrations of oxycodone, noroxycodone, oxymorphone, naltrexone, and 6-β-naltrexol in plasma.

Statistical Method:

CCI [redacted]

Approximately 140 subjects will need to be enrolled in order to ensure that 100 subjects are exposed to at least 2 weeks of treatment with ALO-02 in the Maintenance Phase for the purpose of establishing a safety database. CCI [redacted]

Pharmacokinetic Analysis

Given the expected low fluctuation in steady-state oxycodone concentrations following ALO-02 BID dosing in children and adolescents based on the ALO-02 study B4531006 in adults, the concentrations observed during the Maintenance Phase will be used as an estimate of $C_{ss,av}$ of oxycodone and its metabolites (data permitting) in subjects. The CL/F of oxycodone will be estimated using a ratio of the daily dosing rate of ALO-02 and the estimates of oxycodone $C_{ss,av}$ in the Maintenance Phase. The concentration-time dataset will be analyzed to obtain estimates for V_z/F of oxycodone, data permitting. Covariates of interest (ALO-02 dosage, age, body weight, gender, concomitant medications, etc.) will be evaluated in order to explain the observed between-subject variability in oxycodone $C_{ss,av}$.

Graphical representations and regression analyses may be used to characterize the dose-exposure relationships for oxycodone, naltrexone, and 6-β-naltrexol (data permitting).

Safety Analysis

No formal hypothesis testing of safety data will be performed. The safety population comprises all subjects in the Treatment Period who receive at least one dose of ALO-02. Safety assessments and any adverse events will be presented in tabular and/or graphic form adhering to current Pfizer Data Standards.

Pfizer Data Standards will be used to provide safety summaries on treatment emergent adverse events. In addition, demographics and other safety endpoints (labs, ECG, and vital signs) will be summarized using the following descriptive statistics: N, mean, median, standard deviation, and minimum and maximum for continuous variables, and subject counts and percentages for categorical variables. In particular, presentations for the assessments of objective signs and symptoms of opioid withdrawal (Clinical Opiate Withdrawal Scale; Appendix 8) will be presented in tabular and/or graphic form, adhering to current Pfizer Data Standards.

An Internal Review Committee (IRC) will be established for the purpose of reviewing safety information on an ongoing basis in accordance with Standard Operating Procedures. The IRC will be responsible for ongoing monitoring of the safety of subjects in the study according to the Charter.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the Study Procedures and Assessments sections of the protocol (Section 6 and 7) for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unscheduled visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1. Schedule of Activities

	SCREENING	TREATMENT PERIOD							FOLLOW UP/ POST TREATMENT[19]
		Conversion/Titration Phase (up to 4 Weeks)					Maintenance Phase (2-4 Weeks)		
Visit Identifier	1 (Days -14 to -1)	2 (Day 1)	3a[1] (Day 7)	3b[2] (Day 14)	3c[2] (Day 21)	3d[2] (Day 28)	4 (Day 21, 28, 35 or 42)	5/Early Termination/ End of Study[18] (Day 35, 42, 49 or 56)	6 (Day 28,42,49,56 or 63)
Visit window			±2	±2	±2	±2	±2	±2	±2
Study Entry & Safety Procedures									
Informed Consent/Assent[3]	X								
Inclusion & Exclusion Criteria	X								
Demographics	X								
Medical history	X								
Physical examination	X							X	
Vital signs	X	X	X	X	X	X	X	X	
Clinical laboratory tests (serum chemistry and hematology)	X							X	
Urinalysis (dip stick)	X							X	
Serum pregnancy test[4]	X							X	
Urine pregnancy test[5]		X	X	X	X	X	X		
Contraception Check[20]	X	X	X	X	X	X	X		
Urine drug test (UDT)	X								
Single, 12-lead ECG[6]	X								
Suicide ideation and behavior assessment (C-SSRS)[7]	X	X	X	X	X	X	X	X	X

	SCREENING	TREATMENT PERIOD							FOLLOW UP/ POST TREATMENT[19]
		Conversion/Titration Phase (up to 4 Weeks)					Maintenance Phase (2-4 Weeks)		
Visit Identifier	1 (Days -14 to -1)	2 (Day 1)	3a[1] (Day 7)	3b[2] (Day 14)	3c[2] (Day 21)	3d[2] (Day 28)	4 (Day 21, 28, 35 or 42)	5/Early Termination/ End of Study[18] (Day 35, 42, 49 or 56)	6 (Day 28,42,49,56 or 63)
Visit window			±2	±2	±2	±2	±2	±2	±2
COWS assessment	X	X	X	X	X	X	X	X	
AE assessment[8]	X	X	X	X	X	X	X	X	X
Opioid analgesic review and conversion to ALO-02[9]	X[10]	X[11]							
Concomitant treatments	X	X	X	X	X	X	X	X	
Subject instruction and caregiver training		X							
Dispense ALO-02		X	X	X	X	X	X[12]		
Prescribe rescue medication if necessary		X	X	X	X	X	X	X	
ALO-02 titration visits (as needed)[2]			X	X	X	X			
NRS-Pain scale (in-clinic)		X	X	X	X	X	X	X	
Diary Review[13]									
Pain intensity			X	X	X	X	X	X	
Rescue medication			X	X	X	X	X	X	
Concomitant medication			X	X	X	X	X	X	
Compliance to ALO-02			X	X	X	X	X	X	
AE review			X	X	X	X	X	X	
Pharmacokinetic Assessment									
Plasma samples for PK analyses[14]							X	X[15]	
Other Assessments									
ALO-02 accountability		X	X	X	X	X	X	X	
Early Termination[15, 16]								X	
Weekly telephone call[17]		X	←----------						----------→
Emergency Card	X								

Abbreviations: AE = adverse event; COWS = Clinical Opiate Withdrawal Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; CRF = case report form; ECG = electrocardiogram; NRS = Numerical Rating Scale – Pain; PK = pharmacokinetics; UDT = urine drug test

1. Visit 3a is a mandatory visit.
2. Visits 3b-3d are required only if further dose titrations are required to reach a stable dose. Once a stable dose is achieved the patient is to advance to Visit 4. Subjects must reach a stable dose of ALO-02 on or before Visit 3 to be eligible to start the Maintenance Phase. Unscheduled visits during the Treatment Period for purposes of dose adjustment will, at a minimum, require a NRS-Pain scale and a COWS score on subjects. An unscheduled visit for an AE will require performing the Visit 6 procedures.
3. Informed consent must be provided by the subject's Caregiver [legally acceptable representative/parent(s)/legal guardian]. Subjects are required to provide their assent in compliance with local regulations and IRB requirements.
4. Serum pregnancy test for females of childbearing potential (Section 7.3).
5. Urine pregnancy test for females of childbearing potential (Section 7.3).
6. ECGs performed post-screening are acceptable when performed "for-cause".
7. Refer to Section 7.5.1 for the correct version of Columbia-Suicide Severity Rating Scale (C-SSRS) to administer for a given age group.
8. Report serious adverse events from the signing of the informed consent. AEs are recorded from first dose of ALO-02. Review and transcribe Caregiver adverse findings from the daily Diary to the appropriate CRF.
9. Refer to Appendix 2 of the protocol for the ALO-02 Conversion Guide. The Investigator must calculate the conversion to ALO-02 by Visit 2.
10. Review the subject's pre-study standard of care opioid therapy and record on the appropriate CRF.
11. Pre-study standard of care opioid analgesic is to be discontinued at this visit. Record these changes on the appropriate CRF.
12. Only if at Visit 4 the subject needs an additional 2 weeks of treatment with ALO-02.
13. Review all sections of the daily Diary as part of the Caregiver Training and Subject Instruction. Weekly phone contact between visits to review diary entries. Telephone call must be documented in source documents.
14. Two blood samples for PK analysis will be collected on the same day at least 2 hours apart.
15. PK samples will be collected at Visit 4 or at Early Termination if they are not collected at Visit 4 (Section 7.6.1).
16. All subjects including subjects who discontinue early from the study during the Treatment Period regardless of reason (eg, failure to achieve a stable dose, lack of efficacy, AE) are requested to fulfill the Early Termination procedures and activities (Section 6.2.2).
17. Weekly telephone contact with the caregiver (ie, parent/legal guardian) must be documented in source documents.
18. Subjects who discontinue early from the study as well as subjects who complete 2 weeks of ALO-02 during the Maintenance Phase and have their last dose of ALO-02 at Visit 4 will complete the Visit 5/Early Termination/End-of-Study Visit procedures.
19. The Follow Up/Post Treatment Visit, this may be done over the telephone at the investigator's discretion.
20. The investigator or his/her designee will discuss with the subject/caregiver the need to use highly effective contraception consistently and correctly according to the Schedule of Activities and document such conversation in the subject's chart.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

ALO-02 (PF-06412527) is a combination opioid agonist/opioid antagonist product indicated 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.

ALO-02 capsules consist of controlled-release pellets containing oxycodone hydrochloride (HCl) and naltrexone HCl. Naltrexone HCl is formulated in a 12% (w/w) ratio in combination with oxycodone HCl across all dosage strengths. This abuse deterrent formulation (ADF) uses a proprietary sequestered opioid antagonist platform which is comprised of a sequestered naltrexone core with an outer layer of extended-release (ER) opioid. The first ADF approved in the United States with this technology is EMBEDA®, which consists of morphine sulfate and naltrexone HCl in an ER capsule.[3] The pellet formulation is designed to release oxycodone in an ER manner while retaining naltrexone HCl in the inner core unless the inner core is disrupted. Upon crushing or chewing the pellets, naltrexone is released along with the oxycodone thereby attenuating the liking and euphoric effects of the opioid.

1.2. Background

Moderate-to-severe pain associated with an underlying disease is a common condition among children and adolescents, affecting upwards of 15% to 20% of the pediatric population at one time or another.[4,5] For many children and adolescents, the pain may be untreated or undertreated, resulting too often in prolongation of suffering, disruption of the family routine, and continuation of long-term disability.[5] For the clinician, the management of pain can represent a challenge greater than the treatment of the primary disease itself. Surveys evaluating the pain experience in pediatric patients have shown that children and adolescents can reliably communicate their pain experience by documenting the intensity, duration, and locations of the experience. Consequently, one outcome of better understanding the pain experience in children and adolescents is physician recognition of the need to adequately treat pain in pediatric patients based on the patient's response, as is often done in adult patients experiencing moderate to severe pain.[5,6,7,8,9,10]

1.3. Oxycodone

Oxycodone is a pure opioid agonist available in both immediate release (IR) and ER formulations. Following oral administration of ALO-02 capsules, time to maximum observed oxycodone concentration (T_{max}) is delayed to approximately 12 hours post-dose. Area under the concentration-time curve (AUC) is equivalent and maximum oxycodone plasma concentration (C_{max}) is reduced by approximately 67% when compared with IR oxycodone tablets.[11] When ALO-02 capsules are administered in the fasted state or after a high-fat meal, or when the contents of ALO-02 capsules are sprinkled on applesauce and administered in the fasted state, oxycodone PK are unaffected, yielding similar AUC, C_{max}, and T_{max} values.[12] An analysis of pharmacokinetic results from Phase 1 studies with ALO-02 capsule strengths 20 mg/2.4 mg up to 80 mg/9.6 mg showed that oxycodone AUC and C_{max} increased in a dose proportional manner.[13]

Following intravenous administration, the volume of distribution (V_z) for oxycodone is 2.6 L/kg. Plasma protein binding of oxycodone at 37°C and a pH of 7.4 is about 45%. Oxycodone has been found to be excreted in breast milk.[14]

In humans, oxycodone HCl is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides.[11] CYP3A-mediated N-demethylation to an inactive metabolite form noroxycodone is the principal metabolic pathway of oxycodone in humans. CYP2D6-mediated O-demethylation to an active metabolite oxymorphone is a minor metabolic pathway. Oxymorphone is present in the plasma only in low concentrations.

The total clearance of oxycodone is 0.8 L/min and the apparent elimination half-life ($t_{½}$) following the administration of IR oxycodone is 3.5 to 4 hours. Following oral administration of ALO-02 capsules, the $t_{½}$ of oxycodone is approximately 7.2 hours[8] and steady-state is reached within 48 hours upon twice daily dosing approximately 12 hours apart.[15] Oxycodone and its metabolites are excreted primarily via the kidney.[11] The urinary recovery of total oxycodone (free and conjugated) and its metabolites is approximately 72% of the dose within 48 hours after oral administration.[16]

The PK profiles of oxycodone have been described in adults[17] and in children.[18] Marked differences in PK parameters were observed in infants up to 6 months of age versus adults, and there are some differences in PK parameters in children 2-10 years of age (see Table 2).[14,15,19,20] However, in children and adolescents 7 to 17 years old, no PK differences in oxycodone PK are expected compared to adults.[16]

Table 2. Pharmacokinetic Parameters of Oxycodone after IV Bolus Administration in Children 2-10 Years of Age and Healthy Adults

	$t_{½}$	V_{ss}	CL
Children 2-10 years [a]	1.8±0.4 h	2.1±0.8 L/kg	15.2±4.2 mL/min/kg
Adults	3.7±2.3 h [b]	2.6±0.52 L/kg [b]	780±330 mL/min [b,c]

Abbreviations: CL = renal clearance; IV = intravenous; t½ = elimination half-life; Vss = volume of distribution at steady state
a. Olkkola et al. 1994
b. Poyhia et al. 1991
c. mean body weight 77±11 kg

1.4. Naltrexone

Naltrexone is a synthetic congener of oxymorphone with no opioid agonist activity, but with significant opioid antagonist properties.[21] When ALO-02 capsules are administered in the fasted state or after a high-fat meal, or when the contents of ALO-02 capsules are sprinkled on applesauce and administered in the fasted state, naltrexone plasma concentrations remain undetectable, suggesting that administration of ALO-02 capsules with food or sprinkling of pellets on applesauce does not affect sequestration of naltrexone.[9]

Following oral administration of naltrexone IR tablets, naltrexone undergoes rapid and nearly complete absorption with approximately 96% of the dose absorbed from the gastrointestinal tract. Peak plasma levels of both naltrexone and its major metabolite, 6-β-naltrexol occur within one hour of dosing.[22] The rate and extent of absorption (C_{max} and AUC, respectively)

of naltrexone IR tablets have been shown to increase in a dose proportional manner following oral administration of naltrexone 50 mg tablets as 50 mg, 100 mg and 200 mg doses.

The volume of distribution for naltrexone following intravenous administration is estimated to be 1350 liters.[21] In vitro tests with human plasma show naltrexone to be 21% bound to plasma proteins over the therapeutic dose range. The systemic clearance (after intravenous administration) of naltrexone is ~3.5 L/min, which exceeds liver blood flow (~1.2 L/min). This suggests both that naltrexone is a highly extracted drug (>98% metabolized) and that extrahepatic sites of drug metabolism exist. The major metabolite of naltrexone is 6-β-naltrexol. Two other minor metabolites are 2-hydroxy-3-methoxy-6-β-naltrexol and 2-hydroxy-3-methyl-naltrexone. The activity of naltrexone is believed to be due to both parent and the 6-β-naltrexol metabolite.[23]

In humans, naltrexone is excreted primarily in the urine as conjugates of naltrexone and 6-β-naltrexol. The renal clearance for naltrexone ranges from 30 to 127 mL/min and suggests that renal elimination is primarily by glomerular filtration. In comparison, the renal clearance for 6-β-naltrexol ranges from 230 to 369 mL/min, suggesting an additional renal tubular secretory mechanism. The urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose; urinary excretion of unchanged and conjugated 6-β-naltrexol accounts for 43% of an oral dose. The pharmacokinetic profile of naltrexone suggests that naltrexone and its metabolites may undergo enterohepatic recycling. The mean $t_{½}$ of naltrexone and 6-β-naltrexol are 4 hours and 13 hours, respectively.[21]

1.5. Study Rationale

One of the major challenges facing clinicians who wish to prescribe pain medications to children and adolescents is the paucity of information in the pediatric population about the proper choice of pain medication, dosage guidelines, and expectations with regard to efficacy and untoward effects.[4] This has led to documented cases of overdosing and under-dosing of pain medications in pediatric patients. Efforts to address this challenge include the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), which were enacted by Congress "to promote drug development in children because of the inadequacy of pediatric use information for the majority of drug products approved in the United States".[24]

According to a published Food and Drug Administration (FDA) Workshop on pediatric analgesic trial design "comparatively few children receive around-the-clock opioids for severe pain for time periods of more than 4 weeks".[9] During the past decade, new ER opioid dosage forms have found their way to the market, but with only limited utility and are only infrequently used to manage pain in children and adolescents. An in-house analysis of the Truven (formerly MarketScan) Commercial Claims and Encounters database supplied by Truven Health Analytics from October 2011 through September 2012 included an evaluation of 14 million children from 59.4 million Truven enrollees of which 3,000 (0.02%) received an ER opioid prescription. Of those children receiving an ER opioid prescription, 179 (5.8%) were in the 0-2 years age range, 80 (2.6%) were in the 3-6 years age range, 283 (9.2%) were in the 7-11 years age range, and 2,537 (82.4%) were adolescents in the

12-17 years age range. This study is a post-marketing commitment required by the FDA that will characterize the PK and establish a safety database of ALO-02 in 100 pediatric pain subjects.

The risk to children and adolescents of being on ALO-02 is estimated to be the same as with any other formulations of oxycodone to which patients would already be exposed. Because of the presence of naltrexone in the formulation, a risk could be precipitation of opioid withdrawal if it is released and absorbed. This risk is very low in view of the documented experience in adults showing no definitive withdrawal since, if the formulation is taken as directed, naltrexone absorption is negligible. Analysis from the two Phase 3 studies showed that there was no apparent relationship between naltrexone and 6-β-naltrexol exposure and withdrawal as measured on the Clinical Opiate Withdrawal Scale (COWS). Opiate withdrawal can be immediately treated with good outcome as described in Section 5.3.2.

1.6. Dose Rationale

The dosing recommendation for initiating ALO-02 is based on the dosage guidelines for opioid analgesics in children and adolescents[25,26,27,28] and the growth charts published by the Centers for Disease Control and Prevention (CDC).[29] For example, the recommended starting oral dose of ER oxycodone formulations for opioid-näive children and adolescents in the World Health Organization (WHO) Guidelines[28] is 5 mg every 12 hours for children >8 years of age. Furthermore, the WHO advises that high strength modified-release oxycodone formulations should only be used in patients who are opioid tolerant, as administration of these strengths to non-opioid tolerant patients may cause fatal respiratory depression.[28]

For the IR oxycodone formulation, the WHO recommends starting doses of 0.05-0.125 mg/kg/dose every 4 hours and 0.125-0.2 mg/kg/dose (maximum 5 mg) every 4 hours for opioid-näive and younger children of 1-12 months and 1-12 years of age, respectively.[28] For children 7 years of age, the 3rd percentile of weight distribution is approximately 18 kg.[29] Using a more conservative dosing approach for ALO-02 in pediatric patients the dose in this study should be calculated using 0.05-0.10 mg/kg/dose every 4 hours as a starting dose of oxycodone in children 7 years of age weighing 18 kg. This results in a 5.4 to 10.8 mg total daily dose (TDD) of oxycodone.[30]

For purposes of this study, ALO-02 3 mg oxycodone/0.36 mg naltrexone capsule, 5 mg oxycodone/0.60 mg naltrexone capsule and 15 mg oxycodone/1.8 mg naltrexone capsule will be developed to meet the therapeutic needs of younger and lower weight children.[31] The lower dosing strengths of ALO-02 will allow for the inclusion of opioid experienced as well as opioid naïve children who require around-the-clock treatment with an opioid for moderate-to-severe pain.

1.7. Additional Information

ALO-02 was developed with the goal of decreasing misuse, abuse, and diversion of opioid; an increasing public health problem among many age groups, including adolescents. Non-medical use of opioids has often been associated with prescriptions intended for

legitimate pain patients that are often diverted to unintended users. Approximately 70% of non-medical users of prescription opioids obtain them from friends or relatives.[32] The adolescent group, in particular, has been identified as a population at risk of misuse.[33] ALO-02 will deliver oxycodone as effectively as other long-acting oxycodone preparations while also deterring misuse and abuse because of the presence of the opioid antagonist sequestered in the formulation.

Complete information for ALO-02 may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure (IB).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary

- To characterize the PK of oxycodone in children and adolescents 7 to 17 years of age treated with ALO-02.

- To evaluate the safety of ALO-02 in children and adolescents 7 to 17 years of age.

2.1.2. Secondary

- To determine the systemic exposures of naltrexone and 6-β-naltrexol in children and adolescents 7 to 17 years of age treated with ALO-02.

2.2. Endpoints

2.2.1. Primary

- *Pharmacokinetics:* estimates of oxycodone average steady-state concentration ($C_{ss,av}$) and apparent oral clearance (CL/F).

- *Safety:* incidence, intensity, relationship, and seriousness of adverse events (including symptoms of opioid withdrawal or overdose).

2.2.2. Secondary

- *Pharmacokinetics:* apparent volume of distribution (V_z/F) of oxycodone, data permitting; and systemic exposure levels of the metabolites of oxycodone (oxymorphone and noroxycodone), naltrexone, and 6-β-naltrexol.

- *Safety:* changes in vital signs (blood pressure, heart rate, respiratory rate), clinical chemistry, and hematology laboratory values.

2.2.3. Other

- *Analgesic effect:* pain intensity scores (actual and % change from baseline) and rescue medication or additional analgesic medication use over time.

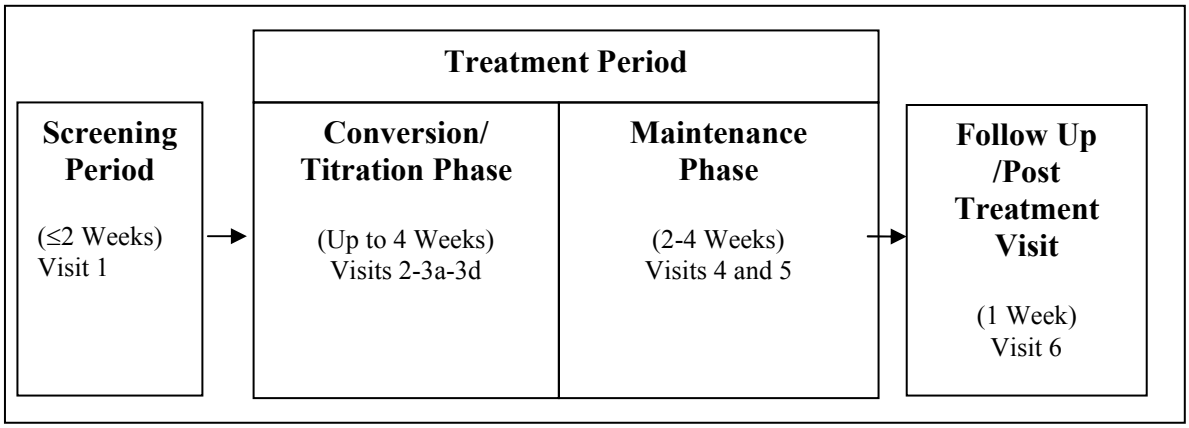
- *Pharmacokinetics:* graphical representations and regression analyses may be used to characterize the dose-exposure relationships for oxycodone, naltrexone, and 6-β-naltrexol.

3. STUDY DESIGN

This is a multicenter, open-label, single-arm study designed to characterize the PK and to evaluate the safety of ALO-02 in children and adolescents 7 to 17 years of age who require opioid analgesia for moderate-to-severe pain. The study consists of 4 study periods occurring over a period of up to 9 weeks (Figure 1) including:

- Screening Period (Visit 1) lasting up to 2 weeks.
- Treatment Period (Visits 2-5) lasting up to 6-8 weeks.
- Follow-Up/Post-Treatment Period (Visit 6) lasting 1 week.

Figure 1. Overall Study Design



The study will enroll approximately 140 children and adolescents between the ages of 7 and 17 years, with at least 100 subjects being exposed to ALO-02 for at least 2 weeks of the Maintenance Phase.[34] Plasma samples will be collected at 2 time points at least 2 hours apart under steady-state conditions from each subject in the two age groups (7-11 years and 12-17 years) to characterize the PK of oxycodone and determine any systemic exposures of naltrexone and 6-β-naltrexol.

3.1. Screening Period

The Screening will occur up to 2 weeks before Visit 2. This period includes one scheduled visit to the study center. The purpose of the Screening Visit is to:

1. Assess a subject's eligibility for study entry;
2. Assess caregiver's willingness and eligibility to meet requirements of the study; and
3. Ascertain a subject's total daily opioid dose (including maintenance opioid and intermittent opioid usage) to guide the conversion from a subject's current opioid therapy to ALO-02 treatment.

3.2. Treatment Period

The Treatment Period duration is 6 to 8 weeks and consists of two phases of variable lengths depending on when a subject achieves a stable dose of ALO-02 and how long opioid analgesia is required.

3.2.1. Conversion/Titration Phase (Visits 2 through 3d)

The goals of the Conversion/Titration Phase are to convert subjects from their pre-study standard of care opioid analgesic to ALO-02 and to individualize pain management by titrating ALO-02 (Visits 2-3d; see Schedule of Activities) to achieve a stable dose. Subjects and their caregiver will report for up to 4 visits during this period. During Visit 2 the subject's study eligibility will be verified, the subject's current standard of care opioid therapy will be discontinued and ALO-02 will be initiated at a dose determined using the ALO-02 Conversion Guide (Appendix 2).

The Conversion/Titration Phase will end once an ALO-02 dose that provides adequate analgesia with minimal adverse reactions is achieved (ie, stable dose) and minimal use of IR oxycodone as rescue, as determined by the investigator. Visit 3a is mandatory for all subjects, while Visits 3b, 3c, and 3d are optional and should be used if additional dose titration is needed. Visits 3b or 3c or 3d can be skipped if a subject reaches a stable dose at a prior visit. When a stable dose is achieved, the subject advances to the Maintenance Phase at the next visit (Visit 4). Subjects who do not reach a stable dose without the need for IR oxycodone as rescue by Visit 3d, will be withdrawn from the study and, if needed, converted to standard of care opioid therapy at the discretion of the investigator.

3.2.2. Maintenance Phase (Visit 4 and Visit 5)

The goal of the Maintenance Phase is to characterize the PK of oxycodone under steady-state conditions, as well as demonstrate the safety of ALO-02 over a 2-week or 4-week period. If at Visit 4 subjects require additional pain relief in the opinion of the investigator, they will continue in the study for an additional 2 weeks and then proceed to Visit 5 (up to 4 weeks total).

During the Maintenance Phase visits are separated by 14 ±2 days. Unscheduled visits are permitted at any time during the Maintenance Phase, as needed, and will follow the procedures outlined in Section 6.7.

Daily Diary and in-clinic pain intensity scores and safety will be assessed at each visit to determine if any dose adjustments are required. Rescue medications (acetaminophen or NSAIDs) are permitted during this phase. IR oxycodone HCl for rescue is discouraged during the Maintenance Phase.

Blood samples will be collected for PK analysis at Visit 4 for those subjects who achieve a stable dose between Visits 3a-3d. Two blood samples will be taken at least two hours apart at Visit 4. If for any reason PK samples are not obtained at Visit 4, the subject should return for an unscheduled visit or no later than Visit 5/Early Termination/End-of-Study Visit.

At Visit 4 or Visit 5, the investigator will discontinue the subject's ALO-02 therapy and, if needed, convert the subject back to standard of care opioid therapy. Blood samples will be collected for PK analysis if not already obtained.

3.2.3. Early Termination Visit

Subjects who do not reach a stable dose at Visits 3a-3d will proceed to the Early Termination Visit. Subjects who do not complete 2-weeks of ALO-02 treatment at their maintenance dose for any reason will proceed to the Early Termination Visit.

All subjects who discontinue early from the study will complete the procedures specified for Visit 5/Early Termination/End-of-Study Visit (see Section 6.2.2).

3.3. Follow Up/Post Treatment Visit

The purpose of the Follow Up/Post Treatment Visit (Visit 6) is to perform final adverse event safety assessments 7±2 days after the last dose of ALO-02 at Visit 5/Early termination/End-of-Study Visit for all subjects and not just for subjects completing Visit 5. The Follow Up/Post Treatment Visit can be done over the telephone at the investigator's discretion.

Subjects who discontinue early from the study as well as subjects who complete 2 weeks of ALO-02 during the Maintenance Phase and have their last dose of ALO-02 at Visit 4 will complete the Visit 5/Early Termination/End-of-Study Visit procedures without the need to return to the clinic for the Follow Up/ Post Treatment Visit.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

4.1. Inclusion Criteria

Subject and caregiver eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects and caregivers are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Male and female subjects aged 7 to 17 years, inclusive.

2. Expected to require (based on the investigator's judgment) continuous around-the-clock opioid treatment equivalent to at least 6 mg total daily dose of oxycodone for the management of moderate-to-severe pain.

3. Treated with opioids for at least 3 consecutive days immediately prior to first day of dosing with at least 6 mg daily dose of oxycodone (or the equivalent if converted from a different opioid the conversion to oxycodone should include a 25-50% dose reduction).

4. Evidence of a personally signed and dated informed consent document indicating that the subject's legally acceptable representative/parent(s)/legal guardian (eg, caregiver) have been informed of all pertinent aspects of the study. Subjects will be required to provide assent in compliance with local regulations and Institutional Review Board (IRB) requirements.

5. Have legally acceptable representative/parent(s)/legal guardian (or adult caregiver) capable of supervising the storage and administration of study drug, and complying with scheduled visits, treatment plan, laboratory tests, and all other study procedures (see Section 4.4).

6. Male subjects able to father children and female subjects of childbearing potential who are sexually active and at risk of pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of ALO-02. Note: this excludes pre-pubertal females (see Section 4.3).

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. A life-expectancy (assessed by investigator) of less than 6 months; or the subject is no longer capable of taking medication orally.

2. History of known hypersensitivity to oxycodone, naltrexone, or opioid products in general. This criterion does not include subjects who have experienced common opioid side effects (eg, nausea, vomiting, and constipation).

3. Respiratory depression and/or unstable, severe bronchial asthma.

4. History of sleep apnea within the past year that would compromise the safety of the subject in the judgment of the investigator.

5. Known or suspected paralytic ileus or any other medical condition that, in the opinion of the investigator, would pose a safety risk to taking ALO-02.

6. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results, and in the judgment of the investigator, would make the subject inappropriate for entry into this study. This may include, but not be limited to, a clinically significant medical condition (eg, cardiovascular, neurological, renal, hepatic, pulmonary, gastrointestinal [including dysphagia], endocrine, hematological, immunological, rheumatological, metabolic, psychiatric) or physical examination, vital signs, ECG, clinical laboratory test abnormalities during screening that, in the judgment of the investigator, would impact the safety of the subject during study participation.

7. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than 3 times the upper limit of normal at the Screening Visit.

8. Surgery within 3 days prior to first day of dosing.

9. Epidural opioid <2 hours prior to the first dose of study drug.

10. Any planned surgery during the course of the study, with the exception of the placement of central or peripheral venous access devices.

11. Subject endorses 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) ideation section or reports any suicidal behavior (Section 7.5.1).

12. Positive urine drug test (UDT) at Screening for any illicit substances or controlled substance medications that have not been prescribed to the subject. An exception to the exclusion for positive opioids, amphetamine, or tetrahydrocannabinol (THC) if written evidence of a valid, current prescription is presented and documented in the source.

13. Pregnant female subjects; breastfeeding female subjects; male subjects with partners currently pregnant; male subjects able to father children and female subjects of childbearing potential who are sexually active and are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after last dose of investigational product or longer based upon the compound's half-life characteristics.

14. Participation in other studies involving investigational drug(s) within 30 days prior to study entry and/or during study participation.

15. Subjects who are children of, or related to, investigational site staff members, site staff members otherwise supervised by the investigator, or Pfizer employees directly involved in the conduct of the study.

4.3. Lifestyle Guidelines

All male subjects who are able to father children and female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of ALO-02. The investigator or his or her designee, in consultation with the subject/caregiver, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his or her partner from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least 1 of the selected methods of contraception. The investigator or his/her designee will discuss with the subject/caregiver the need to use highly effective contraception consistently and correctly according to the Schedule of Activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Pre-pubertal females belonging to Stage 1 on the Tanner scale.

All sexually active male subjects must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose.

4.4. Caregiver(s)

The legally acceptable representative/parent(s)/legal guardian of the subject will actively participate as a caregiver in this study. The caregiver will provide informed consent and also actively participate in the study procedures including the handling, storage, and administration of study drug. The caregiver must be available to be contacted by the study center at least once a week. The role of the caregiver will also include monitoring for signs and symptoms of opioid withdrawal or opioid toxicity and communicating safety information to the investigator (or designee) as appropriate. The investigational site will be responsible for training the caregiver to recognize the signs and symptoms of opioid withdrawal and opioid overdose (see Section 5.2) and to complete a diary on a daily basis during the Treatment and Post-Treatment Periods of the study. The caregiver will be instructed to seek immediate medical attention if signs or symptoms of opioid withdrawal or toxicity occur.

A subject's caregiver(s) must meet all of the following criteria for the subject to be eligible for enrollment into the study:

- Is ≥18 years of age and has demonstrated responsibility as a caregiver through training to:
    - Recognize the signs and symptoms of opioid withdrawal and overdose and recognize the need for immediate medical attention;
    - Administer study drug as directed and record time of each dose of study drug in the diary;
    - Monitor the subject and record observations of adverse events in the diary.
- Is available to accompany the subject to clinic visits.
- Can follow printed instructions in English or Spanish.
- Is willing and able to give written informed consent for the subject.

4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study coordinator's manual or B4531015 study team SharePoint site.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects/caregivers are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it

should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

4.6. Rater Qualifications for Columbia-Suicide Severity Rating Scale (C-SSRS)

Clinic staff administering the assessments and directing the Caregiver in the completion of the Columbia-Suicide Severity Rating Scale (C-SSRS) must be appropriately trained. The risk assessment for the C-SSRS must be done by a clinically qualified child and adolescent mental health professional (MHP). In the United States, in addition to child and adolescent psychiatrists (board certified or board eligible), clinically qualified MHPs include the following: (1) general psychiatrists, (2) licensed Psy.D. or Ph.D. level clinical psychologists, (3) licensed Master's level clinical social workers, or (4) licensed psychiatric nurse practitioners who have training and experience in the diagnosis and treatment of children and adolescents with psychiatric disorders.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

5.1. Allocation to Treatment

All subjects will be treated with ALO-02 capsules for oral use in this single-arm, open-label study.

5.2. Subject Compliance

Subject compliance with ALO-02 will include study drug accountability utilizing capsule count. Dosing will be recorded in the Daily Diary, and discussed at scheduled visits with the caregiver/subject. If a subject's overall medication compliance falls to <70% in any given period between visits, the Investigator or his/her designee will counsel the caregiver/subject on the importance of good compliance and document efforts to improve the subject's compliance. If the subject's compliance does not improve the investigator should consider discontinuing the subject from the study after confirming the decision with Pfizer.

5.3. Opioid Withdrawal and Overdose

5.3.1. Signs and Symptoms of Opioid Withdrawal

Opioid withdrawal is characterized by varying degrees of some or all of the following signs and symptoms in children: increased muscle tone, myoclonus, ataxia, abnormal movements,

pupil dilation (>4 mm), high pitched crying, restlessness, vomiting, poor feeding, diarrhea, tachypnea, yawning, sneezing, hypertension, and mottling.[35]

5.3.2. Management of Opioid Withdrawal

In general, if significant opioid withdrawal occurs, the subject's symptoms may be medically managed with pediatric oral doses of midazolam HCl for anxiety and restlessness (0.25-0.5 mg/kg/dose not to exceed 20 mg/dose),[36] with supplemental doses of IR oxycodone HCl for opioid replacement if necessary, and with oral doses of ondansetron HCl 4 mg every 8 hours as needed[36] to control nausea and vomiting. Otherwise, the subject's symptoms can be treated with careful observation and supportive medical care.

5.3.3. Signs and Symptoms of Opioid Overdose

Acute overdose with oxycodone is manifested by respiratory depression (a decrease in respiratory rate and/or tidal volume, irregular respiration, cyanosis), somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils and, sometimes, shock, convulsions, non-cardiogenic pulmonary edema, pulmonary edema, hypotension, cardiac arrest, and death.[37,38] Marked mydriasis rather than miosis may be seen due to severe hypoxia in some overdose situations.[38]

5.3.4. Management of Opioid Overdose

To treat opioid overdose, primary attention should be given to re-establishment of a patent and protected airway and institution of assisted or controlled ventilation if needed. Other supportive measures (including oxygen, vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

The pure opioid antagonist, naloxone is a specific antidote to respiratory depression resulting from opioid overdose. If needed, the appropriate intravenous dose of naloxone HCl should be administered simultaneously with efforts at respiratory resuscitation at initial dose of 0.01 mg/kg in pediatric subjects weighing less than 20 kg (or younger than 5 years) followed by 0.1 mg/kg if desired clinical response has not been achieved, and 0.01 mg/kg for those weighing more than 20 kg (or older than 5 years) followed by 0.1 mg/kg if desired clinical response has not been achieved up to a total dose of 0.4 mg to 2 mg.[39]

Since the duration of reversal would be expected to be less than the duration of action of oxycodone in ALO-02, the subject must be carefully monitored until spontaneous respiration is readily re-established. ALO-02 will continue to release and add to the oxycodone load for up to 24 hours after administration and the management of overdose should be monitored accordingly. If the response to opioid antagonists is suboptimal or not sustained, additional naloxone should be given as directed by the manufacturer of the product.

Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. Such agents should be administered cautiously to persons who are known or suspected to be physically

dependent on an opioid. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

The sequestered naltrexone in ALO-02 has no role in the treatment of opioid overdose. Investigators may write a prescription for subjects with take-home naloxone auto-injector (Evzio®)[40] for intramuscular/subcutaneous use that the subject and parents/legal guardians can have close by in case an opioid overdose occurs. Evzio is not a substitute for emergency medical care.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

PF-06412527/ALO-02 (oxycodone HCl and naltrexone HCl) capsules are Schedule II (C-II) oral dosage form available in the following strengths: 3 mg/0.36 mg, 5 mg/0.60 mg, 10 mg/1.2 mg, 15 mg/1.8 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg, and 80 mg/9.6 mg. All ALO-02 will be supplied by the sponsor.

ALO-02 will be packaged and provided for use according to the total daily dose requirement as listed in Table 3. No other medications, including rescue medications, will be supplied by the sponsor.

Table 3. ALO-02 Total Daily Dose and Dosing Schedule

Oxycodone HCl Total Daily Dose	ALO-02 Capsule Strength and Dosing Schedule	Conversion/Titration Phase Bottle Pill Count (capsules/bottle)	Maintenance Phase Bottle Pill Count (capsules/bottle)
6 mg	3 mg/0.36 mg BID	20	34
10 mg	5 mg/0.60 mg BID	20	34
20 mg	10 mg/1.2 mg BID	20	34
30 mg	15 mg/1.8 mg BID	20	34
40 mg	20 mg/2.4 mg BID	20	34
60 mg	30 mg/3.6 mg BID	20	34
80 mg	40 mg/4.8 mg BID	20	34
100 mg	20 mg/2.4 mg + 30 mg/3.6 mg BID	40 (blister pack)	72 (blister pack)
120 mg	60 mg/7.2 mg BID	20	34
140 mg	30 mg/3.6 mg + 40 mg/4.8 mg BID	40 (blister pack)	72 (blister pack)
160 mg	80 mg/9.6 mg BID	20	34

5.4.2. Preparation and Dispensing

ALO-02 will be shipped to the study center only after receipt of required documents in accordance with applicable regulatory requirements and sponsor procedures.

ALO-02 must be dispensed and administered according to the procedures described in the protocol. Only subjects enrolled in the study may receive ALO-02 in accordance with all applicable regulatory requirements. Only authorized study center personnel and the caregiver may supply or administer ALO-02. Authorized site personnel will be the investigator (or his/her designee), in accordance with all applicable regulatory requirements.

An Interactive Response Technology (IRT) system will monitor ALO-02 inventory at the study centers and will enact resupply of ALO-02 shipments as necessary.

5.4.3. Administration

ALO-02 is to be administered orally with or without food as per the IB. The bottle label will direct the subject to take 1 capsule orally BID approximately 12 hours apart. Morning doses should be administered between 6:00-10:00 AM every day throughout the study.

When ALO-02 capsules are administered whole, naltrexone HCl remains intact and does not affect the analgesic potential of oxycodone. However, if the capsule is crushed, chewed or dissolved, the naltrexone HCl component is released, competitively binds at the μ-opioid receptors and thus inhibits the effects of the opioid. Therefore, ALO-02 capsules are to be swallowed whole. The pellets in the capsules are not to be crushed, chewed, or dissolved.

As an alternative to taking the capsules whole, and only at the discretion of the investigator, the contents of the ALO-02 capsules (pellets) may be sprinkled over applesauce and then swallowed immediately without chewing. This method of drug administration is only appropriate for children and adolescents unable to swallow capsules, but able to reliably swallow the applesauce without chewing it. The investigator can assess in the clinic, the subject's reliability in swallowing the applesauce without chewing it. Placebo capsules filled with pellets containing sugar spheres and no oxycodone will be provided to the site for this purpose. When using this method, the caregiver should sprinkle the pellets onto a small amount of applesauce (eg, a teaspoonful) and have the child consume the applesauce without chewing it. The child's mouth should then be rinsed (swish and swallow) to ensure that all the pellets have been swallowed. Instructions and training of administering the applesauce will be provided at the clinical site as per the instructions in Pfizer's Investigational Product Manual.

The co-ingestion of ALO-02 with alcohol could result in an increase in oxycodone plasma levels and potentially fatal overdose of oxycodone. Subjects should not consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on ALO-02 therapy.

Misuse of the formulation by tampering (eg, crushing, chewing, or dissolving the contents) may result in the rapid release of both oxycodone and naltrexone, which may lead to fatal respiratory depression or symptoms of significant opioid withdrawal in opioid-tolerant individuals.

Medication errors are reportable irrespective of the presence of an associated adverse event (AE)/serious adverse event (SAE) including:

- Medication errors involving subject exposure to the product.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated AEs are captured on an AE CRF page (refer to ADVERSE EVENT REPORTING section for further details).

5.5. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all ALO-02 capsules are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

ALO-02 is a scheduled, controlled II substance. Study drug is to be stored at 15-25°C and must be secured in a locked cabinet in compliance with all applicable regulatory guidelines for the handling of Schedule II controlled substances. Access must be limited to authorized study personnel only.

Storage conditions stated in the SRSD (eg, IB) will be superseded by the storage conditions stated in the labeling.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor (or designee).

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of ALO-02 receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Once a deviation is identified, ALO-02 must be quarantined and not used until the sponsor provides documentation of permission to use ALO-02. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of ALO-02 prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Study drug, bottles and or blister card must be returned to the investigator at each visit. The investigator is responsible for study drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain study drug accountability records throughout the study. The investigator will return all study drug to the sponsor (or designee).

5.6. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the ALO-02 supplies.

Investigational product accountability forms maintained during the study will be used to support subject dosing data. Study center personnel are responsible for reconciling and resolving discrepancies in ALO-02 accountability. It is the responsibility of the sponsor study monitor (or designee) to review ALO-02 accountability records to ensure that FDA regulations and guidelines concerning investigational product accountability are being adhered to.

Periodic inventories of ALO-02 during and at the end of the study will be performed by the sponsor study monitor (or designee) and the investigator (or designee). Missing ALO-02 must be recorded on the investigational product accountability/return forms along with an explanation of the discrepancy. Missing medication stock must be reported to the sponsor immediately whenever discovered. It is essential that all ALO-02 capsules are accounted for. All unused ALO-02 and bottles will be returned to the sponsor (or designee) after the proper completion of Drug Enforcement Agency (DEA) 222 Form(s).

5.6.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused ALO-02.

5.7. Concomitant Treatments(s)

5.7.1. Permitted Medications and Therapies

Permitted medications and therapies during the study are listed below.

- Acetaminophen and/or NSAIDs as a rescue medication anytime during the Treatment and Post-Treatment Periods at the discretion of the investigator.
    - During the Treatment Period, the use of acetaminophen or non-steroidal anti-inflammatory (NSAID) medications (eg, ibuprofen), as allowed by label for children/adolescents, is permitted as rescue medication, at the discretion of the investigator, at any time in conjunction with ALO-02 to provide pain relief.
- IR oxycodone HCl as a single-entity ingredient (eg, Roxicodone®) as rescue medication at doses prescribed by the investigator during the Conversion/Titration Phase until a stable dose of ALO-02 is achieved. The use of IR oxycodone HCl is discouraged during the Maintenance Phase.
    - The use of IR oxycodone HCl as rescue medication is permitted during the Conversion/Titration Phase at the discretion of the investigator. However, IR oxycodone HCl should be discontinued at the time a stable dose of ALO-02 is determined during the Conversion/Titration Phase.
- Non-opioid adjunct analgesics, bowel regimens, anti-emetics are permitted.

- For any other medications and therapies not listed (eg but not limited to central nervous system (CNS) depressants including sedatives, hypnotics, and other tranquilizer-type drugs) the investigator will consult with Pfizer's clinical team.

5.7.2. Prohibited Medications and Therapies

- Opioid analgesics (including tramadol, tapentadol, buprenorphine) except IR oxycodone HCl used as a rescue medication.
- Mixed opioid agonist-antagonists such as pentazocine, nalbuphine, and butorphanol.
- Monoamine oxidase inhibitors.
- Ethanol in the form of alcoholic beverages (includes medications containing alcohol).

5.8. Rescue Medications

Acetaminophen and/or NSAID medications (eg, ibuprofen) as allowed by label for children/adolescents are permitted as rescue medication, at the discretion of the investigator, at any time in conjunction with ALO-02 to provide pain relief. The dose of acetaminophen in children weighing less than 60 kg is 10-15 mg/kg/dose orally every 4-6 hours as needed or 4000 mg/day, while the dose in adolescents weighing 60 kg or greater is 650 mg to 1000 mg every 4-6 hours as needed not to exceed 4000 mg/day.[41] The dose of ibuprofen in children up to 12 years old is 5-10 mg/kg/dose orally every 6-8 hours as needed with maximum of 4 doses/day, while the dose in subjects 12 years and older is 200 -400 mg orally every 4-6 hours as needed with a maximum of 1200 mg/day.[42] The use of IR oxycodone HCl as a rescue medication is permitted during the Conversion/Titration Phase, at the discretion of the investigator, to aid in the conversion. The use of IR oxycodone HCl is discouraged during the Maintenance Phase. Subjects/caregivers will be required to record use of rescue medication in the diary.

6. STUDY PROCEDURES

Subjects/Caregivers will be asked to complete a diary each day during the Treatment Period of the study.

The investigator and designees are responsible for ensuring that the specified training for completion of the diary is followed for all subjects/caregivers. Training materials will be provided for site staff and caregiver/subjects. During the study, the investigator will review the subject's progress at the time of a subject's study visit.

6.1. Screening Visit (Days -14 to -1)

During the Screening Visit subjects and caregiver(s) will be assessed for study eligibility. This period may last up to 14 days before entering the Treatment Period; however, subjects should be screened as soon as conveniently possible to expedite the Conversion/Titration process. During this visit, the following assessments and procedures will be performed:

- **Informed Consent/Assent:** Subject's legally acceptable representative/parent/legal guardian must sign the informed consent document (ICD). A subject will be required to provide assent in compliance with local regulations and IRB requirements.

- **Inclusion/Exclusion Criteria:** Assess subject against inclusion and exclusion criteria in Section 4.1 and Section 4.2, respectively.

- **Demographics:** Information such as date of birth, race, gender, weight, and height will be collected.

- **Medical history:** Review any significant medical/surgical histories and concurrent illnesses that required or require specialist consultation or treatment.

- **Review of pre-study opioid therapy**: review the subject's opioid therapy and document name of all opioids, dose, and dosing frequency.

- **Concomitant Treatments**: Record all previous medications taken within the last 30 days before screening and concomitant medications (over-the-counter or prescribed. However, if there is a large volume of medications taken in an inpatient setting (such as burn or oncology patients), the requirements for electronic data capture (EDC) entry will be reduced. For subjects that are inpatients at the time of the Screening Visit and prior to enrollment, only opioids, medications for chronic pain, and medications indicated for chronic preexisting conditions will be transcribed onto the respective electronic Case Reprot Form (eCRF). See Section 5.7.

- **Physical examination:** See Section 7.2.6.

- **Vital signs:** Resting blood pressure, heart rate, and respiratory rate.

- **Clinical laboratory testing:** Hematology, blood chemistry, and urinalysis (see Section 7.2.3).

- **Serum pregnancy test:** For all females of childbearing potential (see Section 7.3).

- **Contraception Check.**

- **Urine drug screen:** See Section 7.2.7.

- **Electrocardiogram:** See Section 7.2.4.

- **Suicide Ideation and Behavior Assessment:** Columbia-Suicide Severity Rating Scale (C-SSRS) – Section 7.5.1:

    - Children's Lifetime/Recent (ages 7-11), version 23 Jun 2010 – Appendix 3.

    - Screening (ages 12-17), version 14 Jan 2009 – Appendix 4.

- **COWS:** See Section 7.2.5.
- **Adverse events:** See Section 7.2.1 for reporting of SAEs.
- **Advise** the caregiver that the next visit (Visit 2) is the day when the first dose of ALO-02 will be administered and request that the subject refrains from taking their pre-study opioid on the day of Visit 2. In the event that the opioid has been taken, the visit should be rescheduled for the next day. A telephone call is encouraged the day before Visit 2 to remind the caregiver. Whenever possible, Visit 2 should be scheduled during morning hours.
- Subjects/caregivers are provided with an emergency contact card.

Procedures required by this protocol that were otherwise performed within the last 14 days prior to administration of ALO-02 may be utilized for this study.

6.2. Treatment Period

The Treatment Period will consist of two phases, the Conversion/Titration Phase and the Maintenance Phase. The procedures for each phase are described below.

6.2.1. Conversion/Titration Phase

Visit 2 (Day 1)

During this visit (Study Day 1) the following procedures will be performed before the administration of ALO-02:

- **Vital Signs.**
- **Review** any results from laboratory samples that may exclude a subject from participating.
- **Urine Pregnancy Test:** For all females of childbearing potential.
    - **Suicide Ideation and Behavior Assessment:** C-SSRS – see Section 7.5.1 Children's Since Last Visit (ages 7-11), version 23 Jun 2010 – Appendix 5.
    - Since Last Visit (ages 12-17), version 14 Jan 2009 – Appendix 6.
- **Contraception Check.**
- **COWS assessment.**
- **Pain Numeric Rating Scale (NRS -Pain):** in-clinic assessment.
- **AE assessment:** only pre-dose SAEs will be documented.
- **Review of opioid therapy:** review the subject's opioid therapy and document name of all opioids, dose, and dosing frequency on the appropriate CRF.

- **Concomitant Treatments:** review and document all concomitant medications including dose and frequency.
- **Discontinue pre-study opioid therapy as part of dose conversion**.
- **Dispense ALO-02:** dispense appropriate dose of ALO-02 based on the Conversion Guide as described in Appendix 2.

The following procedures will be performed after dispensing of ALO-02 and after completion of all pre-dose procedures at Visit 2 described above:

- **Subject Instruction and Caregiver Training:** Train the caregiver(s) and instruct the subject on ALO-02 administration and recording of drug accountability, including recording the date/clock time of study drug administration, rescue medication use, analgesia assessments and adverse events between visits in the diary. Administer the first dose of ALO-02 in-clinic and only after the above mentioned procedures are completed.
- **Prescribe Rescue Medication (if needed):** prescribe acetaminophen and/or an NSAID to be used during the Conversion/Titration Phase. IR oxycodone HCL may also be prescribed for rescue with the intent to limit its use until a stable dose of ALO-02 is achieved.
- **Schedule the Visit 3a**.
- Weekly telephone calls to contact the caregiver.

Visit 3a (Day 7±2 days)

All subjects must come to clinic for this visit.

During this visit, the investigator will review the subject's daily diary to assess the subject's pain to determine whether a stable dose of ALO-02 has been achieved (ie, a dose that provides adequate analgesia and minimal adverse reactions).

During this visit the following procedures will be followed:

- **Assess Treatment Response**:
  - Pain intensity (diary review and in-clinic assessment);
  - Rescue medication (diary review);
  - Compliance with ALO-02 (diary review);
  - Concomitant medications (diary review);
  - AEs (diary review).

- **COWS assessment.**
- **NRS-Pain Scale:** in-clinic assessment.
- **Concomitant treatments.**
- **AE assessment.**
- **Vital signs.**
- **Urine pregnancy test:** For all females of childbearing potential.
- **Contraception Check.**
- **Suicide Ideation and Behavior Assessment:** C-SSRS – see Section 7.5.1.
- **ALO-02 Accountability:** see Section 5.5.
- **Dose Titration:** adjust ALO-02 total daily dose as needed to optimize pain therapy.
- **Prescribe Rescue Medication (if needed):** prescribe acetaminophen and/or an NSAID to be used during the Conversion/Titration Phase.
- **Dispense ALO-02** to caregiver.
- Weekly telephone calls to contact the caregiver.

For Converted Subjects: If at Visit 3a the subject has been successfully titrated to a stable dose of ALO-02 and with minimal use of IR oxycodone HCl for rescue, the subject may be scheduled for Visit 4 (see Schedule of Activities and Section 6.2.2). It is at this visit, Visit 3a, that the subject enters the Maintenance Phase of the Treatment Period.

For Non-Converted Subjects: If at Visit 3a the subject **has not** achieved a stable dose of ALO-02, this subject will remain in the Conversion/Titration Phase; therefore, the next visit should be scheduled as described further in the protocol.

ADDITIONAL TITRATION VISITS IF NEEDED

Visit 3b (Day 14 ±2 days)

- Follow the same procedures and assessments as described at Visit 3a.

For Converted Subjects: If at Visit 3b the subject has been successfully titrated to a stable dose of ALO-02 and with minimal use of IR oxycodone HCl for rescue the subject may be scheduled for Visit 4 (see Schedule of Activities and Section 6.2.2). It is at this visit, Visit 3b, that the subject enters the Maintenance Phase of the Treatment Period.

For Non-Converted Subjects: If at Visit 3b the subject **has not** achieved a stable dose of ALO-02, this subject will remain in the Conversion/Titration Phase; therefore, the next visit should be scheduled as described further in the protocol.

Visit 3c (Day 21±2 days)

- Follow the same procedures and assessments as described at Visit 3a.

For Converted Subjects: If at Visit 3c the subject has been successfully titrated to a stable dose of ALO-02 and with minimal use of IR oxycodone HCl for rescue the subject may be scheduled for Visit 4 (see Schedule of Activities and Section 6.2.2). It is at this visit, Visit 3c, that the subject enters the Maintenance Phase of the Treatment Period.

For Non-Converted Subjects: If at Visit 3c the subject **has not** achieved a stable dose of ALO-02, this subject will remain in the Conversion/Titration Phase; therefore, the next visit should be scheduled as described further in the protocol.

Visit 3d (Day 28±2 days)

- Follow the same procedures and assessments as described at Visit 3a.

For Converted Subjects: If at Visit 3d the subject has been successfully titrated to a stable dose of ALO-02 and with minimal use of IR oxycodone HCl for rescue the subject will be scheduled for the next visit, which will be Visit 4 (see Schedule of Activities). It is at this visit, Visit 3d, that the subject enters the Maintenance Phase of the Treatment Period.

For Non-Converted Subjects: If at Visit 3d the subject **has not** achieved a stable dose of ALO-02 the subject will be discontinued from the study and will complete the procedures specified for Visit 5/Early Termination/End-of-Study Visit. The Follow-up/Post Treatment (Visit 6) will be scheduled in one week. ALO-02 will be discontinued, and if needed, converted to a standard of care opioid therapy at the investigator's discretion.

- **Schedule the Follow Up/Post Treatment Visit (Visit 6):** see Section 6.3.

- The Follow-Up/Post Treatment Visit (Visit 6) may be done in the clinic or over the telephone at the discretion of the investigator.

6.2.2. Maintenance Phase

Once the investigator has determined that the subject has achieved a stable dose of ALO-02, the subject will enter the Maintenance Phase of the Treatment Period and be scheduled to return to the study center for Visit 4 two weeks after the last Conversion/Titration Phase visit.

Visit 4

Perform the following assessments:

- **Assess Treatment Response:**

- Pain intensity (diary review and in-clinic assessment);
- Rescue medication (diary review);
- Compliance with ALO-02 (diary review);
- Concomitant medication (diary review);
- AEs (diary review).

- **COWS assessment.**
- **NRS-Pain Scale:** in-clinic assessment.
- **Concomitant treatments.**
- **AE assessment.**
- **Vital signs.**
- **Urine pregnancy test:** For all females of childbearing potential.
- **Contraception Check.**
- **Suicide Ideation and Behavior Assessment:** C-SSRS – see Section 7.5.1.
- **ALO-02 accountability.**
- **Prescribe rescue medication (if needed):** prescribe acetaminophen and/or an NSAID to be used during the Maintenance Phase.
- **Obtain plasma samples for PK analysis:** Record the following items on the appropriate CRF:
  - The exact dosing date and clock times of the previous 4 doses of ALO-02, and
  - The exact clock time of the blood draw for the 2 samples.
- **Dispense ALO-02** to caregiver if the subject needs additional 2 weeks of treatment with ALO-02 and schedule Visit 5/Early Termination/End-of-Study Visit.
- Weekly telephone calls to contact the caregiver.

Visit 5/Early Termination/End-of-Study Visit

Subjects who discontinue early from the study as well as subjects who complete 2 weeks of ALO-02 during the Maintenance Phase and have their last dose of ALO-02 at Visit 4 will

complete the Visit 5/Early Termination/End-of-Study Visit procedures without the need to return for the Follow Up/Post Treatment Visit.

During this visit the following procedures will be followed for all subjects:

- **Physical examination.**
- **Vital signs.**
- **Clinical laboratory testing**.
- **Serum pregnancy test:** for all females of childbearing potential.
- **Contraception Check.**
- **Obtain plasma samples for PK analysis (only if not acquired at Visit 4):** Record the following items on the appropriate CRF:
    - The exact dosing date and clock times of the previous 4 doses of ALO-02, and
    - The exact clock time of the blood draw for the 2 samples.
- **Assess Treatment Response**:
    - Pain intensity (diary review and in-clinic assessment);
    - Rescue medication (diary review);
    - Compliance with ALO-02 (diary review);
    - Concomitant medication (diary review);
    - AEs (diary review).
- **COWS assessment.**
- **NRS-Pain Scale:** in-clinic assessment.
- **Concomitant treatments.**
- **AE assessment.**
- **Suicide Ideation and Behavior Assessment:** C-SSRS – see Section 7.5.1.
- **ALO-02 accountability.**

- **Prescribe rescue medication (if needed):** prescribe acetaminophen and/or an NSAID.
- **Review and document rescue medication use** (name, dose, and frequency).
- Weekly telephone calls to contact the caregiver.

6.3. Early Termination Visit

Subjects who do not reach a stable dose at Visits 3a-3d will proceed to the Early Termination Visit. Subjects who do not complete 2-weeks of ALO-02 treatment at their maintenance dose for any reason will proceed to the Early Termination Visit.

All subjects including subjects who discontinue early from the study will complete the procedures specified for Visit 5/Early Termination/End-of-Study Visit (see Section 6.2.2).

6.4. Visit 6 Follow Up/Post Treatment Visit

The purpose of the Follow Up/Post Treatment Visit (Visit 6) is to perform final adverse event safety assessments. Visit 6 will occur approximately 1 week (7 ±2 days) after discontinuing ALO-02 at Visit 5/Early termination/ End-of-Study Visit for all subjects and not just for subjects completing Visit 5. The Follow Up/Post Treatment Visit can be done over the telephone at the investigator's discretion.

The following procedures are as follows:

- **Suicide Ideation and Behavior Assessment:** C-SSRS – see Section 7.5.1.
- **AE assessment.**

6.5. Subject Withdrawal

Caregivers may withdraw the subject from the study at any time at their own request, or the subject may be withdrawn at any time at the discretion of the investigator or sponsor for safety, including pregnancy, or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site. Subjects who withdraw early from the study during the Treatment Period regardless of reason (eg, failure to achieve a stable dose, lack of efficacy, AE) are requested to fulfill the Early Termination procedures and activities. Should any invasive procedures or new therapies be initiated during the study (eg, nerve block, implanted spinal cord stimulator) the subject may continue at the discretion of the investigator.

Subjects who do not reach a stable ALO-02 dose by Visit 4 (Day 28) will be discontinued from the study. Subjects who test positive for illicit substances on UDT at Screening will be discontinued from the study, unless supported by prescription for medicinal use (eg, ADHD medications or medical marijuana). Those subjects who discontinue the study early and do not complete 2 weeks of the Maintenance Phase should return to the study center as soon as possible for PK sampling and Early Termination procedures.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject/caregiver. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject/caregiver to return all unused investigational product(s), request that the subject/caregiver return for the Early Termination visit, if applicable, and follow-up with the subject/caregiver regarding any unresolved AEs. The clinical staff will make every effort to contact subjects 28 days following their last dose to ascertain health status (ie, AE).

In the event of clinically important treatment-emergent suicidal ideation or suicidal behavior, the subject will be discontinued from the study and will receive the appropriate medical care. The investigator will follow up until the subject's condition has stabilized. Additionally, a risk assessment or evaluation of suicide risk will be completed by a child and adolescent MHP as part of the psychiatric evaluation and assessment of subject safety. Refer to Section 7.5, Assessments. Clinically important suicidality includes but is not limited to:

1. Suicidal behavior (with or without intent of suicide or serious self-harm).

2. Determination of 'yes' on question 4 (Active Suicidal Ideation with Some Intent or Act, Without Specific Plan) for the Suicidal Ideation section of the C-SSRS.

3. Determination of 'yes' on question 5 (Active Suicidal Ideation with Specific Plan and Intent) for the Suicidal Ideation section of the C-SSRS.

4. Determination of 'yes' on the question of Actual Attempt, Interrupted Attempt, Aborted Attempt, or Preparatory Acts or Behavior for Suicidal Behavior section of C-SSRS.

5. Acute suicidality to such a degree that precaution against suicide must be exercised.

6.6. Lost to Follow-Up (LTFU)

A subject will be considered LTFU when one or more Treatment Period visits are missed AND attempts to contact the subject have been unsuccessful leading to an outcome of a missed Visit 5/Early Termination/End-of-Study visit. The following attempts must be made in the order listed below:

1. 3 documented* attempts via telephone; then

2. If feasible, 1 documented* trip by study center personnel to a subject's last known address; then

3. 1 certified, receipted postal letter.

* Receipts, dates and times must be documented in source documents.

Note: A subject who does not return to study but does eventually respond to a site's attempts and is known to be in general good health will be considered as "no longer willing to participate in the study".

6.7. Unscheduled Visits

A subject/caregiver is to contact the study center if the subject is experiencing inadequate analgesia or intolerable opioid or other effects before a scheduled study center visit. If at any time pain worsens despite the use of rescue medication therapy, including IR oxycodone HCl, an unscheduled visit may be needed to adjust the dose of ALO-02. For unscheduled visits due to an increase in pain where titration is necessary, record at a minimum, the Daily Pain Numerical Rating Scale (NRS-Pain) pain and COWS scores on the CRF in addition to any related CRF (eg, concomitant medications, dosing log). An unscheduled visit for any other reason (most typically an AE) will require the Visit 5/Early termination/End-of-Study Visit procedures to be performed (see Schedule of Activities). An unscheduled visit due to a combination of an AE and an increase in pain requires the Visit 5/Early termination/End-of Study Visit procedures.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

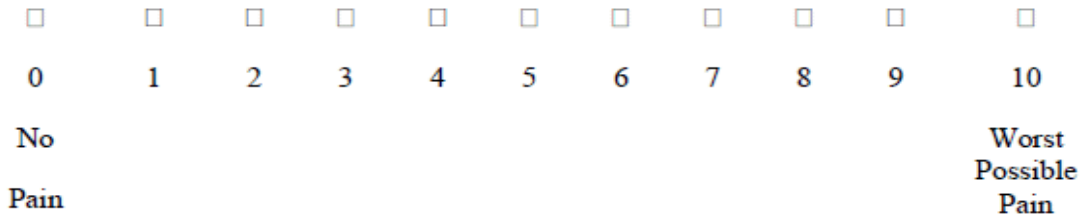
7.1. Analgesic Effect Assessments

7.1.1. Pain Intensity

Daily average NRS-Pain scores will be assessed with an 11-point Numerical Rating Scale ranging from zero (no pain) to 10 (worst possible pain) captured in the diary (Appendix 7). A subject will rate their average pain in the past 24 hours by selecting one number as shown below. The subject will conduct the self-assessment daily with the caregiver(s) in the evening prior to bedtime and record in the diary during the Treatment and Post-Treatment Periods. These diary assessments will be reviewed by the investigator at the in-clinic visits for the purpose of assessing the need for titrating study drug. Pain intensity will also be completed at the in-clinic visits during the Treatment Periods. Only the in-clinic visit pain assessments will be documented on the CRF and used for analysis.

Figure 2. Daily Pain Numerical Rating Scale (NRS-Pain)

Select the number that best describes your average pain in the past 24 hours. (Select one number only).



7.1.2. Rescue Medication Use

The use of rescue medication during the Treatment Period will be recorded in the diary.

The administration of acetaminophen and/or an NSAID during the study is recorded by the caregiver, but is not to be more than labelled and directed by the investigator.

7.2. Safety Assessments

7.2.1. Adverse Events

7.2.1.1. Recording of Adverse Events Using a Diary

The study caregiver (parent or legal guardian) will be instructed on the use of a diary, in which the caregiver will record dosing information, concomitant treatments, and AEs between visits to the clinic. The caregiver will be instructed and details will be provided in written format to the caregiver on the signs and symptoms of opioid overdose (eg, toxicity), opioid withdrawal, as well as other signs and symptoms commonly associated with opioid AEs (eg, nausea, headache, and constipation).

The Clinical Site will contact the caregiver (ie, at least on a weekly basis) to ensure that the caregiver is monitoring for opioid AEs and is recording all relevant AE information in the home diary. All AEs will be brought to the attention of the investigator. The investigator or designee will review and transcribe Caregiver adverse findings for the daily Diary to the appropriate CRF. Weekly telephone contact with the caregiver (ie, parent/legal guardian) must be documented in source documents.

7.2.2. Vital Signs

Vital signs including resting systolic and diastolic blood pressure, heart rate, and respiratory rate are performed at designated study visits as outlined in the Schedule of Activities.

7.2.3. Clinical Laboratory Tests

The hematology, blood chemistry, and urinalysis tests presented in Table are performed at designated study visits as outlined in the Schedule of Activities.

Table 4. Clinical Laboratory Tests

Serum Chemistry	
Alanine aminotransferase (ALT)	Chloride
Albumin	Serum creatinine
Alkaline phosphatase	Creatine phosphokinase
Aspartate aminotransferase (AST)	Glucose
Bicarbonate	Phosphorus
Bilirubin (total)	Potassium
Blood urea nitrogen	Protein (total)
Calcium	Sodium
Cholesterol (total)	
Hematology	
Hematocrit	Red blood cell count
Hemoglobin	White blood cell count
Platelet count	White blood cell differential count (lymphocytes, monocytes, neutrophils, eosinophils, and basophils)
Urinalysis	
Routine dip-stick unless otherwise indicated	
Pregnancy	
Serum and urine hCG	

7.2.4. Electrocardiogram

A single, 12-lead ECG will be performed at Screening for determination of ECG-related eligibility. The ECG should be recorded after subjects have been resting at least 5 minutes in the supine position in a quiet environment. Post-Screening ECGs may be collected if needed (for-cause), at the discretion of the investigator. In the event a clinically significant ECG abnormality is observed on a for-cause ECG, the investigator should consider evaluation of the subject by a cardiologist.

7.2.5. Clinical Opiate Withdrawal Scale (COWS)

Clinical opiate withdrawal is assessed by a clinician-administered instrument, the COWS, at designated study visits as outlined in the Schedule of Activities.

The COWS (Appendix 8) contains 11 common opiate withdrawal signs or symptoms rated by the clinician. The summed score of the 11 items is used to assess a subject's level of withdrawal.[43]

A subject assessed with a COWS score ≥13 will be treated for opiate withdrawal signs and symptoms according to the investigator's medical judgment.

7.2.6. Physical Examination

A physical examination is performed at designated study visits as outlined in the Schedule of Activities. Physical examinations may be conducted by a physician, trained physician's

assistant, or nurse practitioner as acceptable according to local regulation. A complete physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems.

Height and weight is measured only at screening (Visit 1).

7.2.7. Urine Drug Test

A urine drug sample is collected at the Screening Visit, as outlined in the Schedule of Activities, for the purpose of detecting illicit drug substances and/or prohibited analgesic medications (notably opioid analgesics). Certain positive test results may be acceptable providing documentation of a valid prescription is confirmed by the investigator. A positive UDT for cocaine, phencyclidine (PCP), metamphetamine, and ecstasy will disqualify the subject from the study.

Specifically, the following drugs will be screened for by immunoassay by a central laboratory:

- Opioids (codeine, morphine, hydrocodone, hydromorphone, dihydromorphone);
- Oxycodone;
- Methadone;
- Amphetamines (including metamphetamine and ecstasy);
- Phencyclidine (PCP);
- Cocaine;
- THC (marijuana).

7.3. Pregnancy Testing

For female subjects of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at the Screening Visit and End-of-Study Visit, and a urine pregnancy test, with the same sensitivity of at least 25 mIU/mL, will be performed at all other study visits (ie, Visits 2-5). A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the treatment period (or when potential pregnancy is otherwise suspected) and repeated at the end of the study to confirm the subject has not become pregnant during the study. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of ALO-02 but may remain in the study. Pregnancy tests may also be repeated as per request of IRB/Ethics Committees (ECs) or if required by local regulations.

7.4. Contraception Check

The investigator or his/her designee will discuss with the subject/caregiver the need to use highly effective contraception consistently and correctly according to the Schedule of Activities and document such conversation in the subject's chart.

7.5. Suicidality Assessment

7.5.1. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicide ideations and behaviors will be evaluated during all scheduled visits (Visits 1 through 6). The age-appropriate scale must be utilized based upon the subject's age at screening (Visit 1).

For subjects who are between ages 7 and 11:

- The Children's Lifetime/Recent (Version 23 Jun 2010) of the C-SSRS (Appendix 3) should be completed at screening (Visit 1). The Children's Lifetime/Recent scale refers to the subject's lifetime experience. At all study visits after the screening visit, the Children's Since Last Visit (Version 23 Jun 2010) of the C-SSRS (Appendix 5) should be utilized, even if the child has his/her 12th birthday during the study. The Children's Since Last Visit version refers to the subject's experience since the last visit.

For subjects who are between ages 12 and 17:

- The Baseline/Screening (Version 14 Jan 2009) of the C-SSRS (Appendix 4) should be completed at screening (Visit 1). The Baseline/Screening scale refers to the subject's lifetime experience. At all study visits after the screening visit, the Since Last Visit (Version 14 Jan 2009) of the C-SSRS (Appendix 6) should be utilized. The Since Last Visit version refers to the subject's experience since the last visit.

At screening, if the subject endorses a 4 or 5 on the C-SSRS ideation section or reports any suicidal behavior, then the subject is not eligible for study participation and an evaluation of suicide risk (risk assessment) must be completed. Refer to Section 7, Assessments for Details on Risk Assessment.

At every on-site study visit after screening, if the subject endorses a 4 or 5 on the C-SSRS ideation section or reports any suicidal behavior, then the subject must be withdrawn from the study as outlined in Section 6.5, Subject Withdrawal, and an evaluation of suicide risk (risk assessment) must be completed. Refer to Section 7, Assessments for Details on Risk Assessment.

Risk Assessment: In the event that a subject endorses a 4 or 5 on the C-SSRS ideation section or reports any suicidal behavior, an evaluation of suicide risk (risk assessment) completed as part of the psychiatric evaluation and assessment of subject safety to participate will be done by one of the following child and adolescent MHP. In the United States, in addition to child and adolescent psychiatrists (board certified or board eligible), clinically

qualified MHPs include the following: (1) general psychiatrists, (2) licensed Psy.D. or Ph.D. level clinical psychologists, (3) licensed Master's level clinical social workers, or (4) licensed psychiatric nurse practitioners who have training and experience in the diagnosis and treatment of children and adolescents with psychiatric disorders.

Written documentation of the risk assessment should be included in the subject's source documentation, and the risk assessment CRF will be completed. The risk assessment CRF serves as further verification that the psychiatric evaluation and assessment of subject safety has been completed for all subjects endorsing items 4 or 5 on the C-SSRS ideation section or reporting any suicidal behavior. Note: Per protocol, subjects endorsing items 4 or 5 on the C-SSRS ideation section or reporting suicidal behavior at screening are ineligible for study participation. Subjects endorsing items 4 or 5 on the C-SSRS ideation section or reporting any suicidal behavior following the Screening visit must be discontinued from the study and will receive the appropriate medical care. Refer to Section 6.5, Subject Withdrawal.

7.6. Pharmacokinetic Evaluation

7.6.1. Blood Sample Collection and Handling

A total of two 6 mL (2×6 mL) blood samples will be taken for the purpose of quantifying the concentrations of oxycodone, noroxycodone, oxymorphone, naltrexone, and 6-β-naltrexol in plasma. PK samples will be collected at Visit 5 or at Early Termination/End-of-Study Visit if they are not collected at Visit 4. The clock time of the first pharmacokinetic sample will be documented (and noted relative to the clock time of the morning dose of ALO-02) on the CRF. The second pharmacokinetic sample will be drawn at least 2-hours after the first sample and the clock time recorded. Note: The exact dosing date and time for the previous 4 doses of ALO-02 are also to be recorded on the appropriate CRF.

Plasma samples received by the bioanalytical laboratory will be assayed for oxycodone, noroxycodone, oxymorphone, naltrexone, and 6-β-naltrexol using validated analytical methods that conforms with Pfizer's standard operating procedures. All samples collected during the study will be assayed and retained in accordance with local regulations and, if not used (or reused) within this timeframe, will be destroyed. Please refer to the central laboratory procedures manual for collection and storage information.

7.6.2. Plasma Sample Shipment to Bioanalytical Laboratory

The shipping procedures and address of the bioanalytical laboratory will be provided under separate cover.

7.7. Blood Volume

Total blood sampling volume for the individual subject is approximately 36 mL. The actual times of blood sampling may change.

Table 5. Blood Volume

Sample Type	Blood volume (mL)	Number of Sampling Times			Total volume (mL)
		Screening	Treatment Period	End-of-Study	
Safety labs	6	1	--	1	12
Pregnancy[a]	6	1	--	1	12
PK	6		2	--	12
TOTAL	--	--	--	--	36[b]

a. Applies to females of child-bearing age who are sexually active.
b. Total volume does not include discarded blood from pre-draws used to remove fluid from flushed catheters.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

- AEs (serious and nonserious) should be recorded on the CRF from the time the subject has taken at least 1 dose of investigational product through the subject's last visit.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AEs are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Lack of efficacy should be reported as an AE when it is associated with an SAE.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller).

  Concurrent with

- For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, Caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an

AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the

terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also Section 6.5 on Subject Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The caregiver will be questioned about AEs at each visit. The investigator will review the observation log form the diary, and use judgment which observations need to be entered as AEs. The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject/parent(s)/legal guardian/legally acceptable representative. See Section 7.2.1.1 on recording of AEs using Diary.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol for secondary endpoints; any major modifications of the primary endpoint definition and/or its analysis will be reflected in a protocol amendment.

Additional unplanned analyses may be required after all planned analyses have been completed. Any unplanned analyses will be clearly identified in the final clinical study report.

Descriptive summaries for variables measured on a continuous scale will include the mean, standard deviation, median, minimum, and maximum values. Descriptive summaries for variables measured on a categorical scale will include the number and percentage of subjects who presented each value.

9.1. CCI [redacted]

Approximately 140 pediatric subjects will be enrolled in order to achieve that at least 100 children and adolescents are exposed to at least 2 weeks of treatment with ALO-02 in the Maintenance Phase for the purpose of establishing a safety database. At least 25% of children and adolescents will be enrolled in each of the two age groups (7-11 years old and 12-17 years old).

CCI [redacted]

9.2. Efficacy Analysis

Analgesic effect analyses will be performed using all available in-clinic pain intensity data from the safety population in Section 9.4. The baseline pain intensity score will be the score from the in-clinic assessment at Visit 2.

Pain intensity scores will be summarized descriptively by study week and phase of the Treatment Period (Conversion/Titration Phase and Maintenance Phase). Actual scores and the change and percentage change from baseline will be calculated.

Rescue medication or additional analgesic medication use over time will be summarized descriptively.

9.3. Pharmacokinetic Analysis

9.3.1. Pharmacokinetic Analysis Datasets

The PK concentration population is defined as all subjects with at least 1 plasma concentration measurement in this study. The PK analysis population will be defined as all subjects who have usable PK data (ie, concentration data can be associated with the dose level, time of dosing, and time of PK sampling) and are included in the estimates of the primary PK parameters of interest.

9.3.2. Pharmacokinetic Endpoints

Primary PK endpoints will include estimates of oxycodone average steady-state plasma concentration ($C_{ss,av}$) and apparent clearance (CL/F) following treatment with ALO-02. Secondary PK endpoints will include apparent volume of distribution (V_z/F) of oxycodone (data permitting). Endpoints will also include the exposure levels of the metabolites of oxycodone (oxymorphone and noroxycodone), naltrexone, and 6-β-naltrexol following multiple dose treatment with ALO-02. Graphical representations and regression analyses may be used to characterize the dose-exposure relationships for oxycodone, naltrexone, and 6-β-naltrexol (data permitting).

9.3.3. Pharmacokinetic Analysis

Given the expected low fluctuation in steady-state oxycodone concentrations following ALO-02 BID dosing in children and adolescents based on the ALO-02 study B4531006 in adults, the concentrations observed during the Maintenance Phase will be used as an estimate of $C_{ss,av}$ of oxycodone and its metabolites (data permitting) in subjects. The CL/F of oxycodone will be estimated using a ratio of the daily dosing rate of ALO-02 and the estimates of oxycodone $C_{ss,av}$ in the Maintenance Phase. The concentration-time dataset will be analyzed to obtain estimates for V_z/F of oxycodone in subjects, data permitting. Covariates of interest (ALO-02 dosage, age, body weight, gender, concomitant medications etc.) will be evaluated in order to explain the observed between-subject variability in oxycodone $C_{ss,av}$.

The observational data will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum) for the study group as a whole. Graphical representations and regression analyses may be used to characterize the dose-exposure relationships for oxycodone, naltrexone, and 6-β-naltrexol (data permitting).

9.4. Safety Analysis

One safety population is planned consisting of all subjects who participate in the Treatment Period and receive at least one dose of ALO-02.

Safety data will be summarized for the Safety population.

Results from the safety assessments and any adverse events will be presented in tabular and/or graphic form adhering to current Pfizer Data Standards.

Pfizer Data Standards will be used to provide safety summaries on treatment emergent adverse events. In addition, demographics and other safety endpoints (labs, ECG, and vital signs) will be summarized using the following descriptive statistics: N, mean, median, standard deviation, and minimum and maximum for continuous variables, and subject counts and percentages for categorical variables. In particular, presentations for the assessments of objective signs and symptoms of opioid withdrawal (Clinical Opiate Withdrawal Scale; Appendix 8) will be presented in tabular and/or graphic form adhering to current Pfizer Data Standards.

9.4.1. Adverse Events

All AEs will be coded to System Organ Class and Preferred Term (using MedDRA®). Treatment-emergent AEs will be defined as AEs that commence on or after the start of ALO-02 administration. Subjects who have multiple events in the same System Organ Class and Preferred Term in a period will be counted only once at each level of summation (overall, by System Organ Class, and by Preferred Term).

Treatment-emergent AEs will be summarized separately for the Conversion/Titration Phase and the Maintenance Phase (including up to End of Study) by System Organ Class, Preferred Term, maximum intensity, and highest relationship to study drug.

Serious AEs and those leading to study discontinuation will be summarized.

9.4.2. Clinical Laboratory Values

Clinical laboratory data (hematology, chemistry and urinalysis) including changes from Screening will be summarized descriptively by study visit, as applicable.

9.4.3. Electrocardiogram

Electrocardiogram data will be summarized descriptively by study visit, as applicable.

9.4.4. Vital Signs

Vital signs data including changes from Baseline will be summarized descriptively by study visit, as applicable.

9.4.5. Opiate Withdrawal

COWS scores will be summarized descriptively by study visit, as applicable. Additionally, for COWS, the proportion of subjects with mild (COWS Score 5-12), moderate (COWS Score 13-24), moderately severe (COWS Score 25-36), or severe withdrawal (COWS Score >36) will be presented.

9.4.6. Dosing and Compliance

Study drug administration will be summarized descriptively by each subject's mean and median total daily dose and duration of exposure, separately for the Conversion/Titration Phase and Maintenance Phase. There is a permissible 4 hour window within which study

drug can be taken if a drug dose is missed. If later than 4 hours, the subject should be given rescue medication to treat breakthrough pain until the next scheduled dosing time.

9.5. Interim Analysis

No interim analysis is planned for this study.

9.6. Data Monitoring Committee

This study will use an Internal Review Committee (IRC). The IRC will be responsible for ongoing monitoring of the safety of subjects in the study according to the Charter. The recommendations made by the IRC to alter the conduct of the study will be forwarded to the Clinical Lead or delegate for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent/Assent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject's personal data consistent with applicable privacy laws.

The informed consent/assent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

In determining which potential subjects are capable of providing assent, the investigator and/or IRB/EC should take into account the age, maturity, and psychological state of the potential subjects. (The American Academy of Pediatrics advises that assent usually should be obtained from all subjects with an intellectual age of 7 years or more.) If a child or adolescent is legally unable to provide informed consent to participate in the clinical trials, informed consent must be obtained instead from the legally acceptable representative of the child or adolescent, usually their parent(s) or legal guardian, before the child can participate in the study.

Assent is not required if the investigator and/or the IRB/EC determine that the capability of the child or adolescent subject is so limited that they cannot provide assent, or if the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the potential subjects and is available only in the context of the research. In addition, in certain circumstances full informed consent from "emancipated minors" is both necessary and sufficient, rather than assent plus the consent of a legally acceptable representative.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must re-consent as adults to remain in the study. If the enrollment of 'emancipated minors' is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parents(s) or legal guardian and the subject's assent, when applicable before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent/assent document.

12.4. Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial

End of Trial is defined as Last Subject Last Visit and meeting all of the Post-Treatment Period requirements.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of ALO-02 at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 5 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual subjects has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

Abbreviation	Term
ADHD	attention deficit hyperactivity disorder
AE	adverse event
ALO-02	oxycodone hydrochloride and naltrexone hydrochloride extended-release capsules
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID	twice daily
BPCA	Best Pharmaceuticals for Children Act
CDC	Centers for Disease Control and Prevention
C_{max}	maximum (peak) observed drug concentration
C_{ss}	steady state plasma drug concentration
$C_{ss,av}$	average steady state plasma drug concentration
CNS	central nervous system
COWS	Clinical Opiate Withdrawal Scale
CRF	case report form
CSA	clinical study agreement
C-SSRS	Columbia-Suicide Severity Rating Scale
DAI	Drug Administration and Instructions
DEA	Drug Enforcement Agency
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
ER	extended-release
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HRQL	health-related quality of life
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	identification
IND	investigational new drug application
IR	immediate-release
IRB	Institutional Review Board
IRC	internal review committee
IRT	interactive response technology

Abbreviation	Term
IUD	intrauterine device
IVR	interactive voice response
IWR	interactive web response
LFT	liver function test
LPD	local product document
LSLV	last subject last visit
N/A	not applicable
MHP	mental health professional
NRS-Pain	pain numeric rating scale
PCD	primary completion date
PCP	phencyclidine
PREA	Pediatric Research Equity Act
SAE	serious adverse event
SAP	statistical analysis plan
SCL	Supply Chain Lead
SIB	suicidal ideation and behavior
SOP	standard operating procedure
SPC	summary of product characteristics
SRSD	single reference safety document
$t_{½}$	elimination half-life
T_{max}	time to C_{max}
THC	tetrahydrocannabinol
QD	once daily
ULN	upper limit of normal
US	United States
USPI	United States package insert
V_z/F	apparent volume of distribution

Appendix 2. ALO-02 Conversion Guide

While there are useful tables of opioid equivalents readily available, there is substantial inter-patient variation in the relative potency of different opioid drugs and products. As such, it is safer to underestimate a patient's 24 hour oral oxycodone requirement and provide rescue medication (eg, IR oxycodone) than to overestimate the 24-hour oxycodone requirements which could result in adverse reactions.

Investigators should consider the following when using the information in Table 6:

- This is not a table of equianalgesic doses
- The conversion factors in this table are only for the conversion **from** one of the listed oral opioid analgesics **to** ALO-02.
- The table **cannot** be used to convert from ALO-02 to another opioid. Doing so will result in an overestimation of the dose of the new opioid and may result in fatal overdose.
- Follow your established hospital guidelines to convert from intravenous (IV), pain controlled analgesia (PCA) and/or epidural treatment with opioid analgesics before using the oral conversion guidelines in this Appendix.

Table 6. Conversion Factors to ALO-02[1]

Prior Oral Opioid	Approximate Oral Conversion Factor
Codeine (including combination drugs)	0.1
Hydrocodone (including combination drugs)	0.67
Hydromorphone	2.67
Methadone	2 (see note on conversion below)
Morphine	0.67
Oxycodone (including combination drugs)	1
Tramadol	See note on conversion below
Transdermal fentanyl	See note on conversion below

1. Use this formula to calculate total daily dose of ALO-02:
mg/day prior opioid x conversion factor = mg/day ALO-02

Option 1.
To calculate the estimated ALO-02 dose using Table 6:

For subjects on a single opioid, sum the current total daily dose of the opioid and then multiply the total daily dose by the conversion factor listed in Table 6 to calculate the approximate oral oxycodone daily dose.

For subjects on a regimen of more than one opioid, calculate the approximate oral oxycodone dose for each opioid and sum the totals to obtain the approximate total oxycodone daily dose. For subjects on a regimen of fixed-ratio opioid/non-opioid analgesic products, use only the opioid component of these products in the conversion table.

For subjects on around-the-clock opioid who are **not** on oxycodone, reduce the estimated equianalgesic oxycodone total daily dose by 25-50%.

Always round the dose down, if necessary, to the appropriate ALO-02 strength(s) available.

Example conversion from a single opioid to ALO-02:

Step 1: Sum the total daily dose of the prior opioid (for example: extended-release hydrocodone) 30 mg hydrocodone twice daily = 60 mg total daily dose of hydrocodone.

Step 2: Calculate the equivalent dose of oral oxycodone based on the total daily dose of the current opioid using Table 6. In this example, a patient receiving 60 mg total daily dose of hydrocodone × 0.67 (conversion factor) = 40.2 mg of oral oxycodone daily. The total daily dose (40 mg) should then be divided in 2 equal doses; 20 mg twice daily.

Step 3: Reduce the dose by 25-50%. By applying the dose reduction factor of 50% to the above example, the final dosing regimen would be 10 mg/1.2 mg twice daily.

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor subjects for signs and symptoms of opioid withdrawal or for signs of oversedation/toxicity after converting subjects to ALO-02.

Option 2.
Product Specific Conversion Guide:

IMPORTANT INFORMATION ABOUT THIS GUIDE:

Due to incomplete cross-tolerance when converting from a non-oxycodone analgesic to ALO-02, the following equianalgesic conversion tables should be used with some degree of caution. For this reason, it is better to underestimate the subject's 24-hour oral oxycodone requirement and provide rescue medication rather than to overestimate and manage an adverse event.[1]

Conversion from Other Oxycodone Products to ALO-02

OXYCODONE PRODUCTS:

- Combunox® (oxycodone HCl and ibuprofen) Tablets, 5 mg/400 mg.
- OxyContin® (oxycodone HCl controlled-release) Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 160 mg.
- OxyFast® (oxycodone hydrochloride) Oral Concentrate Solution, 20 mg/1 mL.
- OxyIR® (oxycodone hydrochloride) Immediate-Release Oral Capsules, 5 mg.

- Percocet® (oxycodone and acetaminophen tablets, USP) 2.5 mg/325 mg, 5 mg/325 mg, 7.5 mg/325 mg, 10 mg/325 mg, 10 mg/650 mg.
- Percodan® (oxycodone and aspirin tablets, USP) 4.8355 mg/325 mg.
- Tylox® (oxycodone and acetaminophen capsules USP) 5 mg/500 mg.
- Generic equivalent and other immediate-release (IR) products.

HOW TO CONVERT FROM OTHER OXYCODONE PRODUCTS TO ALO-02:

1. Determine the total daily dose of the current opioid therapy being used.
2. Calculate the conversion of the total oral daily dose of the current oxycodone therapy into the equianalgesic dose of oxycodone, using the appropriate ratio (1:1).
3. Refer to the specific analgesic table below to find an equianalgesic dose of ALO-02.
4. Administer the calculated dose in the most convenient dosing strength of ALO-02 in 2 divided doses q12h. ALO-02 should not be given more frequently than every 12 hours.

CONVERTING FROM OTHER OXYCODONE TO ALO-02[10]

Oxycodone daily dose (mg)[a]	**Equianalgesic daily morphine dose (mg)**	**Suggested equianalgesic dose of ALO-02 administered in 2 divided doses q12h (mg)**	**Suggested starting dose of ALO-02 based on existing capsule strengths (mg)**[b]
5	7.5	5	3 BID
10	15	10	3 BID
15	20	15	5 BID
20	30	20	5 BID
30	45	30	5 BID
40	60	40	10 BID
60	90	60	15 BID
80	120	80	40 BID
100	150	100	50 BID

a. Calculate the total daily dose of oxycodone. It may be necessary to start with the lower strength of ALO-02.
b. It is likely that some rescue medication may be needed for breakthrough pain until the dose of ALO-02 can be titrated to the effective daily dose, thus ensuring a smooth transition.
c. There is a lack of systematic evidence bearing on these types of analgesic substitutions. Therefore, specific recommendations are not possible. Healthcare professionals are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate.

TRANSDERMAL FENTANYL PRODUCTS:

- Duragesic® (fentanyl transdermal system) 12.5 mcg/h, 25 mcg/h, 50 mcg/h, 75 mcg/h, 100 mcg/h.

- Generic equivalent.

Conversion From Transdermal Fentanyl To ALO-02

Eighteen hours following the removal of the transdermal fentanyl patch, ALO-02 treatment can be initiated. Although, there has been no systemic assessment of such conversion, a conservative ALO-02 dose, approximately 10 mg/1.2 mg twice daily of ALO-02 should be initially substituted for each 25 mcg/hr fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to ALO-02, as there is limited documented experience with this conversion.

HOW TO CONVERT FROM TRANSDERMAL FENTANYL TO ALO-02

1. Determine the total daily dose of transdermal fentanyl.

   Note that fentanyl is approximately 50 to 150 times more potent than morphine.[5]

2. Calculate the conversion of the total daily dose of the current transdermal fentanyl therapy into the equianalgesic dose of morphine, using the appropriate ratio (based on an approximate equianalgesic ratio of 10:1 for a 10 mcg fentanyl to 1 mg morphine comparison).[6]

3. Refer to the analgesic table below to find the equianalgesic dose of ALO-02. In general, it is safest to give half of the estimated daily ALO-02 demand as the initial dose and to manage inadequate analgesia by supplementation with rescue medication.

4. Administer the calculated dose in the most convenient dosing strength of ALO-02, in 2 divided doses q12h. ALO-02 should not be given more frequently than every 12 hours.

CONVERTING FROM TRANSDERMAL FENTANYL TO ALO-02[5,6,7,8,9]

Transdermal fentanyl daily dose[a]	Equianalgesic morphine daily dose (mg)	Equianalgesic dose of ALO-02 total daily dose (mg)	Suggested starting dose of ALO-02 at ≈50% reduction based on existing capsule strengths(mg)[b]
12.5 mcg/h=300 mcg/day	30	20	5 BID
25 mcg/h=600 mcg/day	60	40	10 BID
50 mcg/h=1200 mcg/day	120	80	20 BID
75 mcg/h=1800 mcg/day	180	120	30 BID
100 mcg/h=2400 mcg/day	240	160	40 BID

a. Calculate the total daily dose of transdermal fentanyl. It may be necessary to start with the lower strength of ALO-02.

b. It is likely that rescue medication may be needed for breakthrough pain until the dose of ALO-02 can be titrated to the effective daily dose, thus ensuring a smooth transition.
c. There is a lack of systematic evidence bearing on these types of analgesic substitutions. Therefore, specific recommendations are not possible. Healthcare professionals are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate.

Conversion from Transdermal Buprenorphine to ALO-02

There has been no systematic assessment of conversion from transdermal buprenorphine to other opioids. Therefore, subjects taking transdermal buprenorphine should be started on ALO-02 dose, 10 mg/1.2 mg twice daily. It is likely that rescue medication may be needed for breakthrough pain until the dose of ALO-02 can be titrated to the effective daily dose, thus ensuring a smooth transition.

Conversion from Tramadol to ALO-02

Because tramadol is not a pure opioid, there has been limited systematic assessment of conversion from tramadol to other opioids.

TRAMODOL PRODUCTS

- Ultram® (tramadol is available in 50 mg, 100 mg, 200 mg and 300 mg strengths).
- Ultram ER® (extended release formulations is available in 100, 200 and 300 mg strengths).
- Ultracet® (tramadol 37.5 mg and acetaminophen 325 mg).
- Generic equivalent and other immediate release (IR) products.

HOW TO CONVERSION FROM TRAMADOL TO ALO-02

1. Determine the total daily dose of tramadol dose.

   Note that morphine is 10-20 times more potent than tramadol.[45]

2. Calculate the conversion of the total daily dose of the current tramadol therapy into the equianalgesic dose of morphine, using the appropriate ratio (based on an approximate oral equianalgesic ratio of 1:10-20).[45]

3. Refer to the analgesic table below to find the equianalgesic dose of ALO-02. In general, it is safest to give half of the estimated daily ALO-02 demand as the initial dose and to manage inadequate analgesia by supplementation with rescue medication.

4. Administer the calculated dose in the most convenient dosing strength of ALO-02, in 2 divided doses q12h. ALO-02 should not be given more frequently than every 12 hours.

CONVERTING FROM TRAMADOL TO ALO-02

Tramadol daily dose (mg)[a]	Equianalgesic morphine dose (mg)	Suggested equianalgesic dose of ALO-02 (mg)	Suggested starting dose of ALO-02 at ≈50% reduction based on existing capsule strengths (mg)[b]
150	15	10	3 BID
200	20	12	3 BID
300	30	20	5 BID
400	40	25	5 BID

a. Calculate the total daily dose of transdermal fentanyl. It may be necessary to start with the lower strength of ALO-02.
b. It is likely that rescue medication may be needed for breakthrough pain until the dose of ALO-02 can be titrated to the effective daily dose, thus ensuring a smooth transition.
c. There is a lack of systematic evidence bearing on these types of analgesic substitutions. Therefore, specific recommendations are not possible. Healthcare professionals are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate.

Conversion from Methadone to ALO-02

Close monitoring is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

METHADONE PRODUCTS:

- Dolophine® Hydrochloride (methadone hydrochloride tablets, USP) 5 mg, 10 mg.
- Methadose® Dispersible Tablets, 40 mg (methadone hydrochloride tablets for oral suspension USP) and Methadone Hydrochloride Tablets USP, 40 mg (dispersible, orange flavored) (methadone hydrochloride tablets for oral suspension USP); Methadose Oral Concentrate (methadone hydrochloride oral concentrate USP) 10 mg/mL; Methadose Sugar-Free Oral Concentrate (methadone hydrochloride oral concentrate USP) dye-free, sugar-free, unflavored, 10 mg/mL.
- Generic equivalent and other immediate-release (IR) products.

HOW TO CONVERT METHADONE TO ALO-02

1. Determine the total daily dose of methadone.
2. Calculate the conversion of the total daily dose of the current methadone therapy into the equianalgesic dose of morphine, using the appropriate ratio (based on an approximate equianalgesic ratio of 1:3-15).[46,47] Calculate the conversion of the total daily dose of the current methadone therapy into the equianalgesic dose of ALO-02, using the appropriate ratio (based on an approximate equianalgesic ratio of 1:2).

3. Refer to the analgesic table below to find the equianalgesic dose of ALO-02. In general, it is safest to give half of the estimated daily morphine demand as the initial dose and to manage inadequate analgesia by supplementation with rescue medication.

4. Administer the calculated dose in the most convenient dosing strength of ALO-02.

CONVERTING FROM METHADONE TO ALO-02[5,46,47,48,49]

Methadone daily dose (mg)[a]	Equianalgesic morphine dose (mg)	Suggested equianalgesic dose of ALO-02 (mg)	Suggested starting dose of ALO-02 at ≈50% reduction based on existing capsule strengths (mg)[b]
10	30	20	5 BID
20	60	40	10 BID
30	90	60	15 BID
40	120	80	20 BID
50	150	100	30 BID
60	180	120	30 BID
80	240	160	40 BID

a. Calculate the total daily dose of methadone. It may be necessary to start with the lower strength of ALO-02.
b. It is likely that rescue medication may be needed for breakthrough pain until the dose of ALO-02 can be titrated to the effective daily dose, thus ensuring a smooth transition.
c. There is a lack of systematic evidence bearing on these types of analgesic substitutions. Therefore, specific recommendations are not possible. Healthcare professionals are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate.

Conversion from Hydrocodone to ALO-02

HYDROCODONE PRODUCTS:

- Lorcet® (hydrocodone bitartrate and acetaminophen tablets USP 10 mg/650 mg); Lorcet® Plus (hydrocodone bitartrate and acetaminophen tablets USP 7.5 mg/650 mg).

- Lortab® (hydrocodone bitartrate and acetaminophen tablets, USP) 5 mg/500 mg, 7.5 mg/500 mg, 10 mg/500 mg; Lortab Elixir (hydrocodone bitartrate and acetaminophen oral solution) 7.5 mg/500 mg per 15 mL.

- Maxidone® (hydrocodone bitartrate and acetaminophen tablets) 10 mg/750 mg.

- Norco® (hydrocodone bitartrate and acetaminophen tablets USP) 5 mg/325 mg, 7.5 mg/325 mg, 10 mg/325 mg.

- Vicodin® (hydrocodone bitartrate and acetaminophen tablets, USP) 5 mg/500 mg; Vicodin ES® (hydrocodone bitartate and acetaminophen tablets, USP) 7.5 mg/750 mg; Vicodin HP® (hydrocodone bitartate and acetaminophen tablets, USP) 10 mg/660 mg.

- Vicoprofen® (hydrocodone bitartrate and ibuprofen tablets) 7.5 mg/200 mg.
- Zydone® (hydrocodone bitartrate and acetaminophen tablets, USP) 5 mg/400 mg, 7.5 mg/400 mg, 10 mg/400 mg.
- Generic equivalent and other immediate-release (IR) products.

HOW TO CONVERT FROM HYDROCODONE TO ALO-02:

1. Determine the total daily dose of hydrocodone.
2. Calculate the conversion of the total daily dose of the current transdermal fentanyl therapy into the equianalgesic dose of morphine, using the appropriate ratio (based on an approximate equianalgesic ratio of 1:1).[10] Calculate the conversion of the total daily dose of the current hydrocodone therapy into the equianalgesic dose of ALO-02, using the appropriate ratio (based on an approximate equianalgesic ratio of 1:0.67).
3. Refer to the analgesic table below to find the equianalgesic dose of ALO-02. In general, it is safest to give half of the estimated daily ALO-02 demand as the initial dose and to manage inadequate analgesia by supplementation with rescue medication.
4. Administer the calculated dose in the most convenient dosing strength of ALO-02, in 2 divided doses q12h. ALO-02 should not be given more frequently than every 12 hours.

CONVERTING FROM HYDROCODONE TO ALO-02:

Hydrocodone daily dose (mg)[a]	**Equianalgesic morphine daily dose (mg)**	**Equianalgesic dose of ALO-02 total daily dose (mg)**	**Suggested starting dose of ALO-02 at ≈50% reduction based on existing capsule strengths (mg)** [b]
20	20	13	3 BID
30	30	20	5 BID
40	40	30	10 BID
60	60	40	10 BID
80	80	60	15 BID

a. Calculate the total daily dose of hydrocodone. It may be necessary to start with the lowest strength of ALO-02.
b. It is likely that rescue medication may be needed for breakthrough pain until the dose of ALO-02 can be titrated to the effective daily dose, thus ensuring a smooth transition.
c. There is a lack of systematic evidence bearing on these types of analgesic substitutions. Therefore, specific recommendations are not possible. Healthcare professionals are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate.

Conversion from Hydromorphone to ALO-02

HYDROMORPHONE PRODUCTS:

- Dilaudid® (hydromorphone hydrochloride) Tablets, 2 mg, 4 mg, 8 mg; Dilaudid Oral Liquid, (5 mg/5 mL).

- Generic equivalent and other immediate-release (IR) products.

HOW TO CONVERT FROM HYDROMORPHONE TO ALO-02:

1. Determine the total daily dose of hydromorphone.

2. Calculate the conversion of the total daily dose of the current hydromorphone therapy into the equianalgesic dose of morphine, using the appropriate ratio (based on an approximate equianalgesic ratio of 1:4).[10] Calculate the conversion of the total daily dose of the current hydromorphone therapy into the equianalgesic dose of ALO-02, using the appropriate ratio (based on an approximate equianalgesic ratio of 1:2.67).

3. Refer to the analgesic table below to find the equianalgesic dose of ALO-02. In general, it is safest to give half of the estimated daily ALO-02 demand as the initial dose and to manage inadequate analgesia by supplementation with rescue medication.

4. Administer the calculated dose in the most convenient dosing strength of ALO-02, in 2 divided doses q12h. ALO-02 should not be given more frequently than every 12 hours.

CONVERTING FROM HYDROMORPHONE TO ALO-02:[10,46,50]

Hydromorphone daily dose (mg)[a]	Equianalgesic morphine dose (mg)	Suggested equianalgesic dose of ALO-02 (mg)	Suggested starting dose of ALO-02at ≈50% reduction based on existing capsule strengths (mg)[b]
6	24	20	5 BID
8	32	20	5 BID
12	48	30	5 BID
16	64	40	10 BID
20	80	40	15 BID
24	96	60	15 BID

a. Calculate the total daily dose of hydromorphone. It may be necessary to start with the lowest strength of ALO-02.
b. It is likely that rescue medication may be needed for breakthrough pain until the dose of ALO-02 can be titrated to the effective daily dose, thus ensuring a smooth transition.
c. There is a lack of systematic evidence bearing on these types of analgesic substitutions. Therefore, specific recommendations are not possible. Healthcare professionals are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate.

Conversion from Morphine to ALO-02

MORPHINE PRODUCTS:

- Avinza® (morphine sulfate extended-release capsules) 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, 120 mg.
- Kadian® (morphine sulfate extended-release) Capsules, 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, 200 mg.
- MS Contin® (morphine sulfate controlled-release) Tablets, 15 mg, 30 mg, 60 mg, 100 mg, 200 mg.
- Oramorph® SR (morphine sulfate) sustained release tablets, 15 mg, 30 mg, 60 mg, 100 mg.
- Generic equivalent and other immediate-release (IR) products.

HOW TO CONVERT FROM MORPHINE PRODUCTS TO ALO-02:

1. Determine the total daily dose of the current opioid therapy being used.
2. Calculate the conversion of the total oral daily dose of the current morphine therapy into the equianalgesic dose of morphine to oxycodone, using the appropriate ratio (1:1.5).[1] Calculate the conversion of the total oral daily dose of the current morphine therapy into the equianalgesic dose of ALO-02, using the appropriate ratio (1:0.67).
3. Refer to the specific analgesic table below to find an equianalgesic dose of ALO-02.
4. Administer the calculated dose in the most convenient dosing strength of ALO-02 in 2 divided doses q12h. ALO-02 should not be given more frequently than every 12 hours.

CONVERTING FROM MORPHINE PRODUCTS TO ALO-02:[10]

Morphine daily oral dose (mg)[a]	Equianalgesic morphine oral dose (mg)	Suggested equianalgesic dose of ALO-02 (mg)	Suggested starting dose of ALO-02 at ≈50% reduction based on existing capsule strengths (mg)[b]
15	15	10	3 BID
30	30	20	5BID
60	60	40	10 BID
90	90	60	15 BID
100	100	60	15 BID
200	200	120	30 BID

a. Calculate the total daily morphine dose. It may be necessary to start with the lowest strength of ALO-02.
b. It is likely that rescue medication may be needed for breakthrough pain until the dose of ALO-02 can be titrated to the effective daily dose, thus ensuring a smooth transition.

c. There is a lack of systematic evidence bearing on these types of analgesic substitutions. Therefore, specific recommendations are not possible. Healthcare professionals are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate.

Appendix 3. Columbia-Suicide Severity Rating Scale (C-SSRS) Children's Lifetime/Recent (Version 6/23/10): Age 7-11

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children`s Lifetime/Recent

Version 6/23/10

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact *posnerk@nyspi.columbia.edu*

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime**	**Past 1 Month**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you ever wish you weren't alive anymore?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you ever decided how or when you would make yourself not alive anymore/kill yourself? Have you ever planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** ***Write response***_____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____	____

Version 6/23/10

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past 3 Months**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you ever <u>do anything</u> to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you ever hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, <u>not at all</u> to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Has subject engaged in Self-Injurious Behavior, intent unknown?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted or Self-Interrupted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted or self-interrupted _____	Yes ☐ No ☐ Total # of aborted or self-interrupted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Appendix 4. Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline/Screening Version (Version 1/14/09): Age 12-17

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***) Past X Months - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___	___

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Appendix 5. Columbia-Suicide Severity Rating Scale (C-SSRS) Children's Since Last Visit (Version 6/23/10): Age 7-11

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Since Last Visit

Version 6/23/10

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103-130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact *posnerk@nyspi.columbia.edu*

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you wish you weren't alive anymore?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you decided how or when you would make yourself not alive anymore/kill yourself? Have you planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** ***Write response***_____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____

Version 6/23/10

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Has subject engaged in Self-Injurious Behavior, intent unknown?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt or Self-Interrupted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted or self-interrupted ____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Appendix 6. Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit (Version 1/14/09): Age 12-17

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted or Self-Interrupted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted or self-interrupted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Appendix 7. Pain Numerical Rating Scale (NRS-Pain)

Question:

Select the number that best described your pain in the past 24 hours. (Select one number only)

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Possible Pain

Appendix 8. Clinical Opiate Withdrawal Scale (COWS)

For each item, check the number that best describes the subject's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the subject was jogging just prior to assessment, the increased pulse rate would not add to the score.

Resting Pulse Rate: _____beats/minute Measured after subject is sitting or lying for one minute ☐0 pulse rate 80 or below ☐1 pulse rate 81-100 ☐2 pulse rate 101-120 ☐4 pulse rate greater than 120	GI Upset: Over last ½ hour ☐0 no GI symptoms ☐1 stomach cramps ☐2 nausea or loose stool ☐3 vomiting or diarrhea ☐5 multiple episodes of diarrhea or vomiting
Sweating: Over past ½ hour not accounted for by room temperature or subject activity. ☐0 no report of chills or flushing ☐1 subjective report of chills or flushing ☐2 flushed or observable moistness on face ☐3 beads of sweat on brow or face ☐4 sweat streaming off face	Tremor: Observation of outstretched hands ☐0 No tremor ☐1 tremor can be felt, but not observed ☐2 slight tremor observable ☐4 gross tremor or muscle twitching
Restlessness: Observation during assessment ☐0 able to sit still ☐1 reports difficulty sitting still, but is able to do so ☐3 frequent shifting or extraneous movements of legs/arms ☐5 unable to sit still for more than a few seconds	Yawning: Observation during assessment ☐0 no yawning ☐1 yawning once or twice during assessment ☐2 yawning three or more times during assessment ☐4 yawning several times/minute

Pupil Size □0 pupils pinned or normal size for room light □1 pupils possibly larger than normal for room light □2 pupils moderately dilated □5 pupils so dilated that only the rim of the iris is visible	Anxiety or Irritability □0 none □1 subject reports increasing irritability or anxiousness □2 subject obviously irritable or anxious □4 subject so irritable or anxious that participation in the assessment is difficult
Bone or Joint Aches: If subject was having pain previously, only the additional component attributed to opiates withdrawal is scored □0 not present □1 mild diffuse discomfort □2 subject reports severe diffuse aching of joints/ muscles □4 subject is rubbing joints or muscles and is unable to sit still because of discomfort	Gooseflesh Skin □0 skin is smooth □3 piloerrection of skin can be felt or hairs standing up on arms □5 prominent piloerection
Runny Nose or Tearing: Not accounted for by cold symptoms or allergies □0 not present □1 nasal stuffiness or unusually moist eyes □2 nose running or tearing □4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing Assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal.