CLINICAL PROTOCOL

AN OPEN-LABEL STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF PF-06412528 IN CHILDREN 7-17 YEARS FOR THE TREATMENT OF MODERATE-TO-SEVERE PAIN

Compound:	PF-06412528
Compound Name:	EMBEDA® (morphine sulfate and naltrexone hydrochloride) Extended Release Capsules
CCI [redacted]	[redacted]
European Clinical Trial Database (EudraCT) Number:	N/A
Protocol Number:	B4541006
Phase:	4

[redacted]

Document History

Document	Version Date	Summary of Changes
Amendment 2	26 May 2015	A substantial change will be preceded by (SC). All other changes are administrative changes as required by the latest protocol template. **Title** **Removed** the word "**chronic**" from the title and throughout the protocol, to improve recruitment by expanding the subject population to subjects with moderate-to-severe post-surgical pain requiring around-the-clock opioid therapy based on investigators feedback. **Protocol Summary** **Endpoints** Primary • (SC) Pharmacokinetics: volume of distribution (Vd/F) deleted and **changed to** "average concentration at steady-state (Css, av)," the low fluctuation in plasma concentration-time profile of morphine and the sparse PK Sampling schedule do not support an estimation of Vd/F analysis. **Study Design** **Added** • Safety Assessment • Pharmacokinetic Assessment • Safety Analysis • Pharmacokinetic Analysis (SC) Pharmacokinetics: Vd/F added here data permitting. **Sections 3.3 and 6.3:** (SC) **Added** PK collections to Visit 6/ET, to accommodate PK sample at early withdrawal if not obtained at Visit 4, which was not provided in Amendment 1. **Section 4.1 Inclusion Criteria** **2.** (SC) "…confirmed moderate-to-severe chronic pain (of cancerous or non-cancerous origin) requiring around-the-clock treatment with an opioid analgesic for an extended period of time." **changed to** "confirmed moderate-to-severe pain requiring around the-clock treatment with an opioid analgesic, "to remove "chronic and allow for the recruitment of post-surgery subjects." **3.** (SC) "…5 consecutive days" **changed to** "3 consecutive days" to expand the subject population and to align with the post-surgical days requirement.

		Most post-surgery subjects will be switched to an extended release opioid within 48 to 72 hours if around-the-clock treatment with an opioid analgesic is required. **Section 4.2 Exclusion Criteria** **8.** (SC) "Undergone major surgery within past 30 days…" **changed to** "…past 3 days….," based on feedback from Embeda investigators, subjects are not likely to be treated with ER opioids for 30 days. **11.** (SC) **Clarified** "subject endorses a 4 or 5 on the Columbia Suicide Severity Rating Scale," to be consistent throughout the protocol. **12.** (SC) **Added** "History of sleep apnea with the past year…, additional safety measure. **13.** (SC) **Added** ALT and AST ≥3 x upper limit of normal.., additional safety measure. **14.** (SC) **Added** "Epidural opioid <2 hours prior to the first dose of study drug," additional safety measure to prevent respiratory depression. **15.** (SC) **Added** "Planned surgery during the course of the study," additional safety measure. **Section 4.3** Life Style Changes wording is **modified**, to adjust the pregnancy wording for the age group of the subjects. **Section 5.2** Subject Compliance wording is **modified,** to set guidelines to aid the investigator. **Section 5.6** Study Drug Accountability is **modified**, to set guidelines to aid the investigator. **Section 5.7** (SC) Concomitant medications **modified,** to clarify allowed and prohibited medications. **Section 6.2** Treatment Periods description is **modified,** to simplify the protocol. **Section 6.3 Addition** and description of Early Termination Visit and Procedures, to ensure final safety assessments are performed and PK sample for subjects who withdraw if not done are obtained. **Section 6.4 Combined** Post Treatment Visit 7 and End of Study Visit 8, to reduce the duration from 21 days to 7 days post the Last Treatment Visit. **Section 6.5** Subject Withdrawal is **modified,** to provide more details to aid investigator in handling subjects who withdraw. **Section 6.6** Lost to Follow-Up is **modified,** to provide more details to aid investigator. **Section 8.4** Medication Errors is **modified and moved**, to provide more clarity. **Section 8.11** Occupational Exposure is **added**, to provide

		guidance for possible AE. **Section 9 Data Analysis/Statistical Methods** (SC) **Deleted "**Unless otherwise indicated, any statistical tests performed will be 2-sided and differences resulting in a p-value ≤0.05 will be considered statistically significant," as there are no statistical analyses performed in the study. **Appendix 1:** Abbreviation table **added** per new template. **Appendix 2: Becomes** Conversion Guide. **Appendix 3: Becomes** C-SSRS Children's Lifetime/Recent. **Appendix 4: Becomes** C-SSRS Baseline/Screening. **Appendix 5:** (SC) C-SSRS Baseline **replaced with** Baseline/Screening. Baseline instrument was inserted in error. **Appendix 6: Becomes** C-SSRS Since Last Visit.
Amendment 1	05 November 2013	Substantial changes reflect 2 points of advice from FDA (letter dated 08/28/2013) from the Division of Anesthesia, Analgesia, and Addiction Products. They are: 1) a minimum requirement of 100 subjects exposed to a minimum of two weeks of PF-06412528 in the Maintenance Phase and 2) Perform the suicidality assessment (ie, C-SSRS) at every scheduled visit. To comply with FDA, Pfizer has modified the Maintenance Phase to 6 weeks, which includes the FDA 2-week minimum as described in the Statistical Analysis Plan and no more than 6 weeks to facilitate recruitment. A substantial change will be preceded by (SC). Administrative changes include any grammatical/syntax and minor clarifying changes pertinent to FDA advice. An administrative non-significant change will be preceded by (NSC). **Protocol Summary** **-Study Design** • Completers defined as subjects completing at least 2 weeks of maintenance treatment for this 6-week study. **--Sample Size Determination** • (SC) Reference to "100 subjects enrolled" **changed to** "140 subjects" to account for a 40% discontinuation rate. • (SC) "An approximately similar number of subjects will be enrolled in each of the two age groups (7-11 years old and 12-17 years old)" **changed to** "…at least 100 subjects completing at least 2 weeks of the Maintenance Phase with neither age group exceeding a 3:1 margin compared to the other age group (7-11 years old and 12-17 years old)." • (SC) "N=50 subjects per age group" **changed to**

		"100 subjects" **--Safety Analysis** • (NSC) Figure 1 **modified to** accommodate FDA advice on shorter study duration. • (SC) Reference to "100 subjects enrolled" **changed to** "140 subjects" to account for a 40% discontinuation rate. • (NSC) Internal Review Committee replaces Data Monitoring Board. **Schedule of Activities** • (NSC) Table modified to accommodate FDA advice on shortening study. **Section 3. Study Design** • (NSC) References to study durations (and table) **modified to** accommodate shortened study. • (NSC) Figure 2 deleted due to complexity in understanding. Schedule of Activities will act in its place. • (SC) Reference to "100 subjects enrolled" **changed to** "140 subjects" to account for a 40% discontinuation rate. **Section 3.2. Treatment Period** • (SC) Stable dose definition refined by adding a time element (5 to 7 days). • (NSC) References to treatment durations **changed from** 12 weeks to 10 weeks. **Section 3.2.1. Conversion/Titration Phase** • (SC) Time element (5 to 7 days) added to stable dose definition. **Section 3.2.2. Maintenance Phase (Visit 4-7 a-c)** • (NSC) "(Visit 4-7 a-c)" in section header **changed to** "(Visit 4-6)". • (NSC) The Maintenance Phase of the study will begin as subjects reach a stable dose of PF-06412528 without the need for immediate-release morphine as rescue and will continue an additional 8 to 11 weeks to ensure that subjects are exposed to a total of 12 weeks of PF-06412528 treatment" **changed to** "The Maintenance Phase of the study will begin as subjects reach a stable dose of PF-06412528 without the need for immediate-release morphine as rescue and will continue an additional 6 weeks to ensure that subjects completed the Treatment Period." • (SC) "To ensure that subjects receive a total of 12 weeks

		of treatment, subjects who reach stable dose at Visit 3a, 3b, 3c or 3d will continue in the study until Visits 7c, 7b, 7b, or 7a, respectively" **changed to** "To ensure that subjects receive a total of 6 weeks of treatment, subjects who reach stable dose at Visit 3a, 3b, 3c or 3d will continue in the study until Visit 6 is completed." • (SC)" During the Maintenance Phase visits are separated by 14 ±2 days, except for subjects who reach a stable dose at Visit 3a, where the interval between Visit 7b and 7c will be only 7 days ±2 days and subjects who reach a stable dose at Visit 3c, where the interval between Visit 7a and 7b will be only 7 days ±2 days." **changed to** During the Maintenance Phase visits are separated by 14 ±2 days." due to visits no longer needed. • (NSC) Unscheduled visits at "Visit 5" **changed to** "Visit 7." • (NSC) "8-11 weeks" **changed** to "6 weeks." to accommodate shortened study. • (NSC) "At the final Maintenance Phase visit (Visit 7a, 7b, or 7c; Day 84 ±2 days), which is contingent on when a subject achieved a stable dose, the investigator will discontinue the subject's PF-06412528 therapy and convert the subject back to their standard of care of opioid therapy. A Post-Treatment visit will be scheduled in 7 ±2 days (Visit 8) and a health status telephone contact (End of Study) will be made 28 ±2 days (Visit 9) following last dose" **changed to** "At the final Maintenance Phase visit (Visit 6), which is contingent on when a subject achieved a stable dose, the investigator will discontinue the subject's PF-06412528 therapy and convert the subject back to their standard of care of opioid therapy. A Post-Treatment visit will be scheduled in 7 ±2 days (Visit 7) and a health status in-clinic or telephone contact (End of Study) will be made 28 ±2 days (Visit 8) following last dose." **Section 3.3 Post-Treatment Period** • (NSC) Visit 8 changed to Visit 7. **Section 3.4 End of Treatment Period** • (NSC) Header **changed to** "End of Study Period". • (NSC) "Visit 9" **changed to** "Visit 8". **Section 4.1. Inclusion Criteria** • (SC) #3: "Be an experienced opioid user, defined as any subject who has been on around-the-clock opioid therapy, equivalent to ≥20 mg per day of morphine, for a period of at least 2 weeks immediately prior to Screening" **changed to** "Be an experienced opioid user, defined as any subject

		who has been on around-the-clock opioid therapy, equivalent to ≥20 mg per day of morphine, for a period of 5 consecutive days immediately prior to Screening."
		
		Section 4.6 Rater Qualifications
		• (SC) New section added for C-SSRS assessments.
		
		Section 5.3.3. Administration
		• (NSC) Reference to DAI manual for instructions on how to administer study drug via apple sauce.
		
		Section 5.5.2. Prohibited Medications and Therapies
		• (SC) Added the exception that the use of IR morphine in the Maintenance Phase would be acceptable. Rationale: any exacerbation of pain where IR morphine would be needed will not be a reason to discontinue subject.
		
		Section 6 Study Procedures
		• Subjects/caregivers will be asked to complete a diary each day in the evening before going to bed during the Conversion/Titration Phase of the study **changed to** subjects/caregivers will be asked to complete a diary each day during the Treatment and Post-Treatment Phases of the study. Rationale: No time element for completing the diary. Only the pain NRS was required to be recorded at bedtime in the diary.
		
		Section 6.1. Screening Period (Day -14 to -1)
		• (SC) The phrase of "Suicidality Assessment" **changed to** "Suicide Ideation and Behavior (SIB)" Assessment.
		  • Added C-SSRS Children's Lifetime/Recent".
		  • Added C-SSRS Screening version (for 12-17 years).
		
		Section 6.2.1 Conversion/Titration Phase
		• (SC) Added "Suicide Ideation and Behavior (SIB) Assessment": Columbia-Suicide Severity Rating Scale (C-SSRS) -(Section 7.4.1):
		  • Children's Since Last Visit (Ages 7-11) (Version 6/23/10)-(Appendix 4).
		  • Baseline (Ages 12-17) (Version 1/14/09)-(Appendix 5).
		
		Visit 3a (Day 7 ±2 Days)
		• (SC) Added "Suicide Ideation and Behavior (SIB) Assessment": Columbia-Suicide Severity Rating Scale (C-SSRS) -(Section 7.4.1):
		  • Children's Since Last Visit (Ages 7-11)

		(Version 6/23/10)-(Appendix 4). • Since Last Visit (Ages 12-17) (Version 1/14/09)-(Appendix 6). **Visit 3b (Day 14 ±2 Days)** • (SC) Added "Suicide Ideation and Behavior (SIB) Assessment": Columbia-Suicide Severity Rating Scale (C-SSRS) -(Section 7.4.1): • Children's Since Last Visit (Ages 7-11) (Version 6/23/10)-(Appendix 4). • Since Last Visit (Ages 12-17) (Version 1/14/09)-(Appendix 6). • (NSC) Section for Converted Subjects: "Visit 4 (Day 21)" **changed to** "Day 28". **Visit 3c (Day 21 ±2 Days)** • (SC) Added "Suicide Ideation and Behavior (SIB) Assessment": Columbia-Suicide Severity Rating Scale (C-SSRS) -(Section 7.4.1): • Children's Since Last Visit (Ages 7-11) (Version 6/23/10)-(Appendix 4). • Since Last Visit (Ages 12-17) (Version 1/14/09)-(Appendix 6). • (NSC) Section for Converted Subjects: "Visit 4 (Day 21)" **changed to** "Day 35". **Visit 3d (Day 28 ±2 Days)** • (SC) Added "Suicide Ideation and Behavior (SIB) Assessment": Columbia-Suicide Severity Rating Scale (C-SSRS) -(Section 7.4.1): • Children's Since Last Visit (Ages 7-11) (Version 6/23/10)-(Appendix 4). • Since Last Visit (Ages 12-17) (Version 1/14/09)-(Appendix 6). • (NSC) Section for Converted Subjects: "Visit 4 (Day 21)" **changed to** "Day 42". **Section 6.3. Maintenance Phase** **Visit 4 (Day 21 ±2 days, Day 28 ±2 days, Day 35 ±2 days, or Day 42 ±2 days** • (SC) Added "Suicide Ideation and Behavior (SIB) Assessment": Columbia-Suicide Severity Rating Scale (C-SSRS) -(Section 7.4.1): • Children's Since Last Visit (Ages 7-11)

		(Version 6/23/10)-(Appendix 4). • Since Last Visit (Ages 12-17) (Version 1/14/09)-(Appendix 6). **Visit 5 (Day 35±2 days, 42±2 days, 49±2 days, or 56±2 days)** • (SC) Added "Suicide Ideation and Behavior (SIB) Assessment": Columbia-Suicide Severity Rating Scale (C-SSRS)-(Section 7.4.1). • Children's Since Last Visit (Ages 7-11) (Version 6/23/10)-(Appendix 4). • Since Last Visit (Ages 12-17) (Version 1/14/09)-(Appendix 6). **Visit 6 (Day 49±2 days, 56±2 days, 63±2 days, or 70±2 days)** • (SC) Added "Suicide Ideation and Behavior (SIB) Assessment": Columbia-Suicide Severity Rating Scale (C-SSRS)-(Section 7.4.1). • Children's Since Last Visit (Ages 7-11) (Version 6/23/10)-(Appendix 4). • Since Last Visit (Ages 12-17) (Version 1/14/09)-(Appendix 6). **(SC) Due to FDA advice on shortening the study Visits 7a, 7b, 7c were deleted. Visit 7 is now included under Section 6.4 Post-Treatment period.** **Section 6.4 Post-Treatment Period** • (NSC) Visit 8 **change to** Visit 7 (56±2 days, 63±2 days, 70±2 days, or 77±2 days). • (SC) Deleted 12-lead ECG. Rationale: Will insert into protocol "for-cause" only. • (SC) Deleted Urine Drug Test as it has no value at this time point. • (SC) Added "Suicide Ideation and Behavior (SIB) Assessment": Columbia-Suicide Severity Rating Scale (C-SSRS) -(Section 7.4.1): • Children's Since Last Visit (Ages 7-11) (Version 6/23/10)-(Appendix 4). • Since Last Visit (Ages 12-17) (Version 1/14/09)-(Appendix 6). • (SC) added "in-clinic" pain intensity score. • (NSC) Added "Assess Treatment Response" to match Schedule of Activities.

		Section 6.5. End of Study Period • (NSC) Visit 9 (Day 112±2 days or 28±2 Days After Last Dose) **changed to** Visit 8 ((Day 77±2 days, 84±2 days, 91±2 days or 98±2 days. **Section 6.6. Subject Withdrawal** • (SC) Added protocol-specific language for suicide ideation/behavior. **Section 7.1.1. Pain Intensity** • (NSC) Appendix 3 **changed to** Appendix 7 due to addition of C-SSRS. **Section 7.1.2. Rescue Medication Use** • (SC) Added that rescue medication will be recorded in Maintenance Phase as well. **Section 7.2.4. Electrocardiogram** • (SC) Added new wording for how to perform the ECG. **Section 7.2.5. Clinical Opiate Withdrawal Scale (COWS)** • (NSC) Appendix 4 **changed to** Appendix 8. **Section 7.2.7. Urine Drug Test** • (SC) Added that an opioid finding at the Screen and Baseline visits is an expected results due to a subject still taking their SOC medication. An illicit drug finding is a reason to screen fail a subject. **Section 7.3. Pregnancy Testing** • (SC) Urine pregnancy test at Visits 2-7 **changed to** Visits 2-6 due to shortened study. **Section 7.4.1. Columbia-Suicide Severity Rating Scale (C-SSRS)-Lifetime** • (SC) Entire section replaced with revised section due to FDA advice. **Section 7.5.1. Blood Sample Collection and Handling** • (SC) Second bulleted paragraph devoted to collection procedures and storage temperatures deleted due to the procedures not validated for morphine. Reader is referred to the central laboratory procedure manual for mixing and storage information. **Section 9.1. Sample Size Determination** • "The study plans to enroll 100 pediatric subjects for the purpose of establishing a safety database, with as many

		subjects as possible being exposed to 12 weeks of therapy with PF-06412528 and an approximately similar number of subjects enrolled in each of the two age groups (7-11 years old and 12-17 years old)" **changed to "**The study plans to enroll approximately 140 subjects for the purpose of establishing a safety database, with at least 100 subjects completing at least 2 weeks of the Maintenance Phase with neither age group exceeding a 3:1 margin compared to the other age group (7-11 years old and 12-17 years old)". **Section 9.6. Data Management Committee** • (SC)All references to Data Monitoring Committee or DMC change to Internal Review Committee or IRC, respectively. **Appendices** • All reordered due to addition of C-SSRS instruments.
Original Protocol	11 April 2013	N/A

PROTOCOL SUMMARY

Background and Rationale:

PF-06412528 capsules consist of controlled-release pellets containing morphine sulfate and naltrexone hydrochloride. The pellets are designed to release morphine in an extended-release manner over time while retaining naltrexone, a mu-opioid antagonist, in the inner core unless the inner core is disrupted. Upon crushing or chewing the pellets, naltrexone is released along with the morphine thereby attenuating the liking and euphoric effects of the opioid. CCI [redacted] The drug was developed with the potential to decrease the misuse, abuse, and diversion of prescription opioids, a public health problem among many age groups including adolescents.

One of the major challenges facing clinicians who wish to prescribe pain medications to children 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) and the Pediatric Research Equity Act (PREA).

The use of morphine to treat pain in pediatric patients with cancer is well recognized. However, the increasing use of morphine in children to treat other forms of moderate to severe pain (eg, neurological pain) has become apparent only during the past decade. During that same period, new extended-release opioid dosage forms have found their way to the market with only limited information about their use in pediatric patients. Therefore, in addition to meeting regulatory requirements, there is an unmet therapeutic need to research the safe and effective use of all extended-release opioid products in children. The present study is intended to evaluate the safety and characterize the pharmacokinetics (PK) of PF-06412528 in children 7 to 17 years of age who require opioid analgesia for moderate-to-severe pain.

Objectives:

Primary

- To demonstrate the safety of PF-06412528 in children 7 to 17 years of age treated with PF-06412528 for moderate-to-severe pain.
- To characterize the PK of morphine in children 7 to 17 years of age treated with PF-06412528 for moderate-to-severe pain.

Secondary

- To determine the exposures of naltrexone and 6-β-naltrexol in children 7 to 17 years of age treated with PF-06412528 for moderate-to-severe pain.

Endpoints:

Primary

- *Safety:* incidence, intensity, relationship, and seriousness of adverse events (including symptoms of opioid toxicity or withdrawal) during treatment with PF-06412528.
- *Pharmacokinetics:* population PK of morphine apparent clearance (CL/F) and average concentration at steady-state ($C_{ss, av)}$ following treatment with PF-06412528.

Secondary

- *Safety:* changes in vital signs (pulse rate, blood pressure, respiratory rate), clinical chemistry, and hematology laboratory values.
- *Pharmacokinetics:* morphine apparent volume of distribution (Vz/F, data permitting) and *systemic* exposure levels of the metabolites of morphine (morphine-3-glucuronide [M3G] and morphine-6-glucuronide [M6G]), naltrexone, and 6-β-naltrexol, following multiple-dose treatment with PF-06412528.

Other

- *Analgesic Effect:* pain intensity scores (Appendix 7); actual and percentage 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 morphine, naltrexone, and 6-β-naltrexol data permitting.

Study Design:

This is a multicenter, 6-week, open-label, single-arm study to demonstrate the safety and characterize the PK of PF-06412528 in children 7 to 17 years of age, with moderate-to-severe pain. The study will enroll approximately 140 children to obtain at least 100 subjects exposed to study treatment for at least 2 weeks in the Maintenance Phase. Plasma samples will be collected during the Maintenance Phase at 2 time points under steady-state conditions to characterize the PK of morphine and determine the systemic exposures of naltrexone and 6-β-naltrexol.

Assessments:

Safety Assessments

Before admission to the study, subjects will undergo a physical examination and a round of testing procedures/measurements including 12-lead electrocardiogram (ECG), blood pressure, pulse rate, respiratory rate, and clinical and laboratory testing. During the study,

the investigator will pay close attention to monitoring for adverse events including, but not limited to, opioid overdose (toxicity) and/or signs and symptoms of opioid withdrawal.

Pharmacokinetic Assessments

Once the subjects have achieved a stable dose of PF-06412528, two blood samples will be taken at two time points post-dose at least two hours apart during Visit 4 to characterize the PK of morphine and its metabolites and determine the exposure levels of naltrexone and 6-β-naltrexol.

Statistical Method:

Sample Size Determination

The study plans to enroll approximately 140 subjects for the purpose of establishing a safety database, with at least 100 subjects exposed to study drug for at least 2 weeks in the Maintenance Phase with neither age group exceeding a 3:1 margin compared to the other age group (7-11 years old and 12-17 years old). Likewise, the study plans to evaluate the PK of morphine in all subjects that provide plasma samples. CCI

Pharmacokinetic Analysis

Given the very low fluctuation in steady-state morphine concentrations following PF-06412528 BID dosing, the concentrations observed during the Maintenance Phase will be used as an estimate of $C_{ss,av}$ of morphine and its metabolites (data permitting) in pediatric subjects. The CL/F of morphine will be estimated using a ratio of the daily dosing rate of PF-06412528 and the estimates of morphine $C_{ss,av}$ in the Maintenance Phase. The concentration-time dataset will be analyzed to obtain estimates for Vz/F of morphine in pediatric subjects, data permitting. Covariates of interest (PF-06412528 dosage, age, body weight, gender, concomitant medications etc) will be assessed for their ability to account for the observed variability in morphine $C_{ss,av}$.

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

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 PF-06412528. 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 (AE). 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 (COWS); 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 STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to titrate study drug or conduct evaluations/assessments required to protect the wellbeing of the subject.

Periods		Screening (2 Wks)	Treatment								Post-Treatment Follow Up/ /EOS (Clinic) (1 Wk)
			Conversion/Titration Phase (1 to 4 Wks)					Maintenance Phase (2-6 Wks)			
Scheduled Visits	Visit	1	2	3a [1]	3b [2]	3c [2]	3d [2]	4	5	6/ET	7
	Day ±Allowable Window	-14 to -1	1	7±2	NR	NR	NR	21±2	35±2	49±2	56±2
					14±2	NR	NR	28±2	42±2	56±2	63±2
						21±2	NR	35±2	49±2	63±2	70±2
							28±2	42±2	56±2	70±2	77±2
Activities											
Informed Consent/Assent [3]		X									
Inclusion/Exclusion Criteria (Sections 4.1 and 4.2)		X									
Demographics		X									
Medical History		X									
Opioid Therapy Review		X[4]	X[5]								
Safety	Physical Examination (Section 7.2.6)	X								X	
	Clinical Laboratory Tests (Section 7.2.3)	X								X	
	Pregnancy Test (Section 7.3)	X[6]	<----------X[7] ---------->							X[6]	
	Urine Drug Test (Section 7.2.7)	X									
	Single, 12–lead ECG [8] (Section 7.2.4)	X									
	Vital Signs (Section 7.2.2)	X	X	X	X	X	X	X	X	X	
	Suicide Ideation and Behavior (SIB)	X	X	X	X	X	X	X	X	X	X

Periods		Screening (2 Wks)	Treatment							Post-Treatment Follow Up/ /EOS (Clinic) (1 Wk)
			Conversion/Titration Phase (1 to 4 Wks)					Maintenance Phase (2-6 Wks)		
Scheduled Visits	Visit	1	2	3a [1]	3b [2]	3c [2]	3d [2]	4	5	6/ET	7
	Day ±Allowable Window	-14 to -1	1	7±2	NR	NR	NR	21±2	35±2	49±2	56±2
					14±2	NR	NR	28±2	42±2	56±2	63±2
						21±2	NR	35±2	49±2	63±2	70±2
							28±2	42±2	56±2	70±2	77±2
Activities											
	Assessment[9] (Section 7.4.1)										
	COWS (Section 7.2.5)	X	X	X	X	X	X	X	X	X	
	Concomitant Medication (Section 5.7)	X	X	X	X	X	X	X	X	X	
	Adverse Events[10] (Section 7.2.1)	X	X	X	X	X	X	X	X	X	X
Treatment Response	Pain Intensity (In-Clinic) (Section 7.1.1)		X	X	X	X	X	X	X	X	
	Review Diary Information[11]			X	X	X	X	X	X	X	
	Pain Intensity (Diary Review)			X	X	X	X	X	X	X	
	Rescue Medication (Diary Review)			X	X	X	X	X	X	X	
	Concomitant Medication (Diary Review)			X	X	X	X	X	X	X	
	Study Drug Use (Diary Review)			X	X	X	X	X	X	X	
	Adverse Events (Diary review)			X	X	X	X	X	X	X	
	Plasma Sample (Section 7.5.2)[12]							X		X[13]	
Caregiver Training and Subject Instruction			X								
Dose Conversion Calculation[13]			X								
Dispense Study Drug			X	X	X	X	X	X	X		
Prescribe Rescue Medication (as necessary)			X	X	X	X	X	X	X	X	
Dose Titration (as needed)				X	X	X	X				
Drug Accountability				X	X	X	X	X	X		
Early Withdrawal Subjects[13,15]										X	
Weekly Telephone call[16]			<----------								---------->

Min = Minimum; Max = Maximum; NR = Not Required; EOS = End of Study; ECG = Electrocardiogram; ET = Early Termination; COWS = Clinical Opiate Withdrawal Scale; PK = Pharmacokinetics, Wks= Weeks

1. Visit 3a is a mandatory visit.
2. Visits 3b, 3c, and 3d are required only if further dose titrations are required to reach a stable dose. Subjects must reach a stable dose of PF-06412528 on or before Visit 3d to be eligible to start the 6-week 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 (parent or legal guardian). Subjects are required to provide their assent.
4. Review the subject's pre-study standard of care (SOC) therapy and record on the appropriate case reporting form.
5. SOC therapy is required to stop on this visit. Record these changes on the appropriate case reporting form.
6. Serum pregnancy test for a qualified female of childbearing potential (Section 7.3).
7. Urine pregnancy test for a qualified female of childbearing potential (Section 7.3).
8. ECGs performed post-baseline are acceptable when performed "for-cause".
9. Refer to Section 7.4.1 for the correct Columbia-Suicide Severity Rating Scale to apply for a given age group.
10. Record serious adverse events from the signing of the informed consent. Non-serious AEs are recorded from first dose of study drug. Review and transcribe Caregiver adverse findings from the Daily Diary to the appropriate case reporting form. Follow up on all SAEs through and including 28 calendar days post the last dose of study drug (Section 8.2). Follow up requirements for non-serious AEs (Section 8.1).
11. Review all sections of the Daily Diary as part of the Caregiver Training and Subject Instruction. Issue a new diary at each scheduled visit. Weekly phone contact between visits to review diary entries. Call must be documented in source.
12. Two plasma samples for PK analysis will be collected at least 2 hours apart.
13. Request PK samples (Section 7.5.1) of early termination subjects if not acquired at Visit 4.
14. Consult Appendix 2 of the protocol for the PF-06412528 Conversion Guide. The investigator must figure the conversion to PF-06412528 by Visit 2.
15. Subjects prematurely withdrawing from the Treatment Period regardless of reason (eg, failure to achieve a stable dose, lack of efficacy, AE) are requested to fulfill the Visit 6 procedures and activities. Early withdrawal subjects will be converted back to their pre-study SOC medication or alternate pain therapy, at the discretion of the investigator.
16. Weekly telephone contact with the caregiver must be documented in source.

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APPENDICES

1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-06412528 (morphine sulfate and naltrexone hydrochloride) is a combination opioid/antagonist controlled-release 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. Currently, the product is approved for adult use only.

PF-06412528 is not intended to be used for acute pain, as an as needed (prn) analgesic, or for pain that is mild or does not persist for an extended period of time.

1.2. Background

Moderate to severe pain associated with an underlying disease is a common complaint among children, affecting upwards of 15% to 20% of the pediatric population at one time or another.[1,2] Unfortunately, for many children, pain may be untreated or undertreated, resulting too often in prolongation of suffering, disruption of the family routine, and continuation of long-term disability.[2] For the clinician, the management of pain can represent a greater challenge than the treatment of the primary disease itself. Surveys evaluating the pain experience in pediatric patients have shown 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.[2,3,4,5,6,7]

PF-06412528 capsules consist of controlled-release pellets containing morphine sulfate and naltrexone hydrochloride. The pellets are designed to release morphine in an extended-release manner over time while retaining naltrexone, a mu-opioid antagonist, in the inner core unless the inner core is disrupted. Upon crushing or chewing the pellets, naltrexone is released along with the morphine thereby attenuating the liking and euphoric effects of the opioid. CCI [redacted]

The study is being conducted as a Phase 4 post-marketing requirement by the Food and Drug Administration (FDA) consistent with ICH E11 guidelines for "Clinical Investigation of Medicinal Products in the Pediatric Population."

1.3. Morphine

The pharmacokinetics of morphine in PF-06412528 are characterized by a relatively slow absorption phase and prolonged pharmacokinetic disposition phase compared with an immediate-release (IR) formulation (oral morphine solution).[8] Approximately 20 to 40% of an oral dose reaches the systemic circulation within 30 minutes following administration of an oral solution, compared with 8 hours following administration of an equivalent dose of PF-06412528. Once absorbed, morphine is distributed to major organ systems throughout the body including the brain. However, while the central nervous system (CNS) represents

the primary site of action for the drug, only small quantities of morphine cross the blood brain barrier. Morphine is extensively metabolized, primarily via glucuronidation, to multiple metabolites including morphine-3-glucuronide, M3G (approximately 50%) and morphine-6-glucuronide, M6G (approximately 5 to 15%), which are then largely excreted in the urine. In adults, the mean plasma clearance of morphine is approximately 20 to 30 mL/min/kg.[8] The half-life of morphine is reportedly 2 hours following intravenous administration but significantly more prolonged following oral administration of a controlled-release product.

In pediatric patients, the PK of morphine have been characterized in infants, pre-term infants, and neonates, usually following parenteral administration of morphine.[9,10] In older children, the PK of morphine have been characterized following oral therapy with morphine for cancer pain.[11] The latter PK study was conducted in 40 children whose median age was 11.4 years (range 1.7 to 18.7 years). Morphine sulfate was administered orally as either an IR liquid or sustained-release tablets at an average daily dose of 35 mg (1.4 mg/kg/day). For the pediatric group as a whole, the population PK estimates of morphine apparent clearance and volume of distribution were 23.1 mL/min/kg and 5.2 L/kg, respectively. Of interest, the apparent clearance of morphine was on average 1.7-fold higher in the group of children <11 years of age (n=18; mean age 6.3 years, range 1.7 to 9 years) compared with the children >11 years (n=22; mean age 13.8 years, range 11 to 18.7 years) making up the older group (37.4 mL/min/kg versus 21.9 mL/min/kg). The average half-life of morphine for the pediatric group as a whole was 2.3 hours. The analgesic properties of morphine in children and dosing guidelines for oral and parenteral administration have also been described in the literature.[3,12]

1.4. Naltrexone

Naltrexone is a mu opioid antagonist. While absorbed orally, the drug is subject to significant first-pass metabolism, with absolute bioavailability estimates ranging from 5 to 40%. Both parent drug and active metabolite (6-β–naltrexol) contribute to the mu-opioid antagonistic activity of naltrexone. Likewise, both parent drug and active metabolite are excreted in the urine (53% to 79% of the dose). The elimination half-life of naltrexone is approximately 4 hours.

Under normal dosing conditions with PF-06412528, clinical studies have shown that there is minimal systemic exposure of naltrexone when taken as directed. In adult patients titrated up to 120 to 160 mg of PF-06412528 per day, naltrexone levels in the range of 4 to 26 pg/mL were detected under steady-state conditions.[8] In a long term study, with PF-06412528 doses up to 860 mg administered twice daily, approximately 11% of blood samples taken pre-dose at steady state had detectable concentrations of naltrexone in plasma from 4 to 145 pg/mL. There were no adverse events associated with these clinically insignificant concentrations among the population of opioid-dependent patients with chronic pain. However, under conditions in which PF-06412528 is chewed or crushed, up to 100% of the sequestered naltrexone dose could be released from the formulation, with a naltrexone exposure level comparable to that of an IR oral solution of the same dose.

1.5. Additional Information

PF-06412528 was developed with the potential to decrease misuse, abuse, and diversion; a recently increasing public health problem among many age groups including adolescents. Non-medical use of opioids has often been associated with legitimate prescriptions. The adolescent group, in particular, has been identified as a population at risk of misuse.[13] Theoretically, PF-06412528 will deliver morphine as effectively as other long-acting morphine preparations while also deterring misuse and abuse because of the presence of the opioid antagonist sequestered in the formulation.

Complete information for PF-06412528 may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator's Brochure.

1.6. Study Rationale

One of the major challenges facing clinicians who wish to prescribe pain medications to children 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. This has led to documented cases of overdosing and under dosing pain medications in pediatric patients.[1] 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".[14]

While the use of morphine to treat pain in pediatric patients with cancer is well recognized, its use to treat other forms of moderate-to-severe pain (eg, arthritis, neuropathic pain) has become apparent only during the past decade. During that same period, new extended-release opioid dosage forms have found their way to the market, but with only limited utility. According to a published Food and Drug Administration (FDA) Workshop on pediatric analgesic trial design, "comparatively few children receive round-the-clock opioids for severe pain for time periods more than 4 weeks."[6] An in-house analysis of 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 PF-06412528 in 100 pediatric pain subjects.

Moreover, the results of this in-house analysis also revealed that very few children (6.1%) treated with opioids take them chronically and even fewer (2.1%) are treated with a long-acting opioid. Therefore, this study will establish a safety database and characterize the pharmacokinetics of PF-06412528 in 100 children with moderate-to-severe pain, as required.

Although chronic opioid use is not common in children, this study is meant to provide valuable safety and PK data on this new formulation of morphine with possible abuse-deterrent properties as a benefit to patients and the community in hopefully achieving an incremental advance in addressing abuse, misuse, and diversion. The benefit of having additional PK, safety, and dosing data for children with this new formulation is also a critical reason for obtaining these data. The risk to the children is estimated to be the same as with other formulations of morphine to which these patients would already be exposed as they are opioid-dependent. The additional risk could be precipitation of opioid withdrawal. This risk is very low in view of the documented experience in adults showing no definitive withdrawal if the formulation is taken as directed. Withdrawal can be immediately treated with good outcome as described in Section 5.1.5.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary

- To demonstrate the safety of PF-06412528 in children 7 to 17 years of age treated with PF-06412528 for moderate-to-severe pain.
- To characterize the pharmacokinetics of morphine in children 7 to 17 years of age treated with PF-06412528 for moderate-to-severe pain.

2.1.2. Secondary

- To determine the systematic exposures of naltrexone and 6-β-naltrexol in children 7 to 17 years of age treated with PF-06412528 for moderate-to-severe pain.

2.2. Endpoints

2.2.1. Primary

- *Safety:* incidence, intensity, relationship, and seriousness of adverse events (including symptoms of opioid toxicity or withdrawal) during treatment with PF-06412528.
- *Pharmacokinetics:* population pharmacokinetic estimates of morphine apparent clearance (CL/F) and average steady-state concentration ($C_{ss,av}$) following treatment with PF-06412528.

2.2.2. Secondary

- *Safety:* changes in vital signs (pulse rate, blood pressure, and respiratory rate), clinical chemistry, and hematology laboratory values.
- *Pharmacokinetics:* apparent volume of distribution (Vz/F) of morphine, data permitting; and systemic exposure levels of the metabolites of morphine (morphine-3-glucuronide [M3G] and morphine-6-glucuronide [M6G]), naltrexone, and 6-β-naltrexol.

CCI

[redacted]

3. STUDY DESIGN

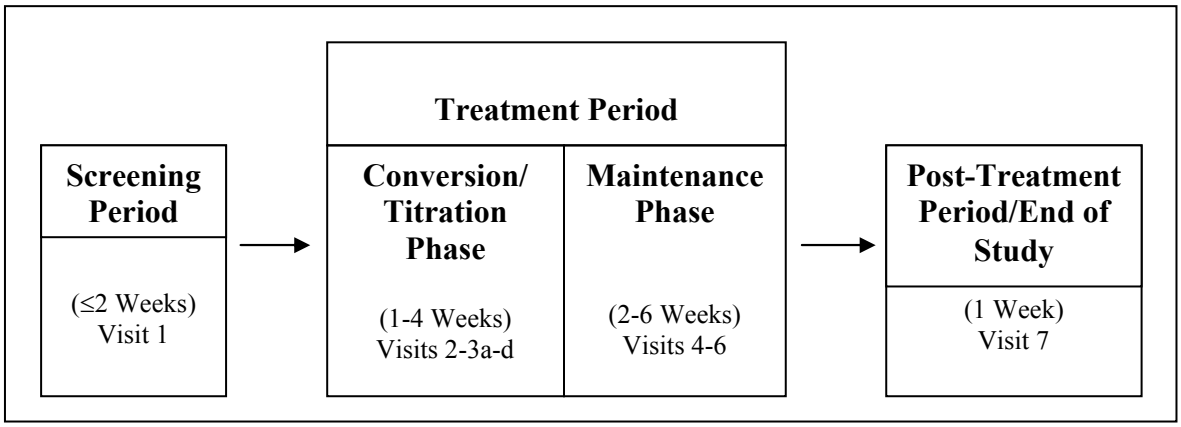
This is a multicenter, 6-week, open-label, single-arm study to demonstrate the safety and characterize the PK of PF-06412528 in children 7 to 17 years of age, with moderate-to-severe pain.

Subjects must be taking opioids prior to entry into the study. Initial PF-06412528 dosage will be determined by the subject's pre-study opioid treatment prior to the Conversion/Titration Period.

The study consists of 3 study periods (Figure 1) including:

- Screening Period (Visit 1) lasting up to 2 weeks.
- Treatment Period (Visits 2-6) lasting up to 10 weeks.
- Post-Treatment Period/End of Study Period (Visit 7) lasting 1 week.

Figure 1. Overall Study Design



The study will enroll approximately 140 children between the ages of 7 and 17 years with at least 100 subjects exposed to study treatment for at least 2 weeks in the Maintenance Phase. Plasma samples will be collected at 2 time points under steady-state conditions from each subject in the two age groups (7-11 years and 12-17 years) to characterize the pharmacokinetics of morphine and determine the systemic exposures of M3G, M6G, naltrexone and 6-β-naltrexol.

Opioid naïve subjects will not be enrolled in the study.

3.1. Screening Period

The Screening Period occurs up to 2 weeks. This period includes one scheduled study center visit. The purpose of the Screening Period is:

1. To assess a subject's initial eligibility for study entry;

2. To assess caregiver(s) willingness and initial eligibility to meet their requirements of the study; and

3. To 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 PF-06412528 treatment.

3.2. Treatment Period

The Treatment Period will be conducted using an open-label, non-randomized, single-arm study design to demonstrate the safety and characterize the pharmacokinetics of PF-06412528 under multiple dose conditions.

The Treatment Period duration is 7 to 10 weeks and consists of two phases of variable lengths depending on when a subject achieves a stable dose of PF-06412528; a Conversion/Titration Phase lasting up to 4 weeks and a Maintenance Phase lasting up to 6 weeks. The purpose of the Conversion/Titration Phase is to convert subjects from their current opioid therapy to PF-06412528 using a standardized conversion guide (see

Appendix 2), and individualize subjects' pain management by titrating with PF-06412528. The purpose of the Maintenance Phase is to maintain the subject on a stable dose of PF-06412528 up to an additional 6 weeks, if possible, such that a subject could potentially be exposed to up to 10 weeks of treatment with PF-06412528.

During the Treatment Period, safety, pain intensity and pharmacokinetics will be assessed.

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

Subjects and their caregiver(s) will report for weekly visits during this 1-4 week period to convert their current standard of care opioid therapy for pain management to PF-06412528. The goals of the Conversion/Titration Phase are to convert subjects from their pre-study standard of care opioid analgesic to PF-06412528 and to individualize pain management by titrating PF-06412528 (Visits 2-3d; see Schedule of Activities) to achieve a stable dose. A stable dose is characterized as a dose that provides adequate analgesia and minimizes adverse reactions for 5 to 7 days. During Visit 2 the subject's study eligibility will be verified, the subject's current standard of care opioid therapy will be discontinued and PF-06412528 will be initiated at a dose determined using the PF-06412528 Conversion Guide (Appendix 2).

Four weekly scheduled study visits (Visits 3a-3d) are planned to provide enough time to individualize pain management with PF-06412528. Visit 3a is mandatory for all subjects and Visits 3b, 3c, and 3d are optional, 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). More frequent consultation with the investigator as well as additional unscheduled clinic visits are permitted, as needed (eg, to titrate study drug). All information about the dosing of PF-06412528 (ie, dosage strength, frequency of dosing, and daily schedule) will be obtained and recorded at each scheduled/unscheduled visit.

The Conversion/Titration Phase will end once a PF-06412528 dose that provides adequate analgesia and minimizes adverse reactions is achieved (ie, stable dose) with infrequent need for IR morphine as rescue as determined by the investigator. Subjects who do not reach a stable dose without the need for IR morphine as rescue by Visit 3d, will be removed from treatment and converted back to their previous opioid therapy or another therapy at the discretion of the investigator.

The start of the Maintenance Phase will begin once a subject has achieved a stable dose of PF-06412528 and the next study visit (Visit 4) will be scheduled in two weeks' time.

3.2.2. Maintenance Phase (Visit 4 – 6)

The goal of the Maintenance Phase is to characterize the PK under steady-state study conditions as well as demonstrate the safety of PF-06412528 over a 2-6 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 2-4 weeks (Visit 5 and/or Visit 6) up to 6 weeks total.

Daily Diary and in-clinic pain intensity and safety will be assessed at each visit to determine if any dose adjustments are required. Rescue medication (acetaminophen and/or NSAID's) is permitted during this phase. IR morphine for rescue is discouraged during the Maintenance Phase.

Blood samples will be collected for PK analysis at Visit 4 for those subjects that achieve a stable dose between Visits 3a-d. 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 to enable them to be obtained at an unscheduled visit.

At the final Maintenance Phase visit (Visit 4 or 5 or 6), the investigator will discontinue the subject's PF-06412528 therapy and convert the subject back to their standard of care of opioid therapy. Blood samples will be collected for PK analysis if not already obtained. A Post-Treatment/End of Study visit will be scheduled in 7 ±2 days (Visit 7).

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 PF-06412528 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 6/Early Termination (Section 6.3).

3.3. Post-Treatment Period/End of Study Period

The purpose of the Post-Treatment Period/End of Study (Visit 7) is to perform safety assessments 7 ±2 days after the last dose of PF-06412528 at Visit 6.

Subjects who discontinue early from the study as well as subjects who complete 2 weeks of PF-06412528 during the Maintenance Phase and have their last dose of PF-06412528 at Visit 4 will complete the Visit 6/Early Termination procedures without the need to return for the Post Treatment/End of Study 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 protocol treatment is considered appropriate. All relevant medical and non-medical 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 appropriately qualified 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. Subjects between the ages of 7 and 17 years, inclusive, at the time of enrollment.

2. Having confirmed moderate-to-severe pain requiring around-the-clock treatment with an opioid analgesic.

3. Be an experienced opioid user, defined as any subject treated with opioid therapy, equivalent to ≥20 mg per day of morphine, for a period of 3 consecutive days immediately prior to first day of dosing with PF-06412528.

4. Have parental/guardian (or adult caregiver) capable of providing informed consent, supervising the storage and administration of study drug, and complying with scheduled visits, treatment plan, and all other study procedures (see Section 4.4).

5. Evidence of a personally signed and dated informed consent document indicating that the subject's parent or legal/parental/guardian (eg, caregiver) has 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.

6. Male subjects able to father children and female subjects of childbearing potential who are sexually active and at risk for 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 PF-06412528.

7. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

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 is no longer capable of taking medication orally.

2. Pregnant female subjects; breastfeeding female subjects; or male subjects with partners currently pregnant.

3. History of known hypersensitivity to morphine, naltrexone, or opioid products in general.

4. Participation in other studies involving investigational drugs within 30 days prior to study entry and/or study participation.

5. Significant respiratory depression and/or severe bronchial asthma.

6. Known or suspected of having paralytic ileus or has any other medical condition that, in the opinion of the investigator, would pose a safety risk to taking PF-06412528.

7. Have other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study treatment 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.

8. Undergone surgery within 3 days prior to the first day of dosing.

9. Positive urine drug test (UDT) at Screening for any illicit or scheduled drug not prescribed for the subject.

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

11. Subject endorses a 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS) ideation section or reports any suicidal behavior. (Section 7.4.1).

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

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

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

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

4.3. Life Style 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 28 days after the last dose of study drug. The investigator or his or her designee, in consultation with the subject, will confirm an appropriate method of contraception for the individual subject 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 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:

- 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.
- Correctly placed copper containing intrauterine device (IUD).
- Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, suppository).
- 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 study drug and continuing for at least 28 days after the last dose.

4.4. Caregiver(s)

The parent or legal guardian of the subject will actively participate as caregiver in this study. As caregiver, the parent or legal guardian will not only provide informed consent, but 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 include monitoring for signs and symptoms of opioid toxicity or opioid withdrawal and communicating safety information to the investigator or designee as appropriate. The investigational site will be responsible for training the caregiver and subject, when appropriate, to recognize the signs and symptoms of opioid toxicity and opioid withdrawal (see Section 5.1.1) and to complete a diary on a daily basis during the Treatment and Post-Treatment Periods of the study. The caregiver/subject will be instructed to seek immediate medical attention if signs or symptoms of opioid toxicity or withdrawal 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 toxicity and withdrawal and recognize the need for immediate medical attention;

- Administer study drug as directed and record time of each dose of study drug;
- 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 trial is documented in the study contact list located in the coordinator's manual or team SharePoint site.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, subjects 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 number 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 only be used 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 study team or 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

Clinic staff administering the assessments and directing the caregiver in the completion of the Columbia-Suicide Severity Rating Scale (C-SSRS) must be trained. The risk assessment for the C-SSRS must be done by a clinically qualified child and adolescent Mental Health Provider (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) 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 drug 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 PF-06412528 (morphine sulfate and naltrexone hydrochloride) extended-release capsules for oral use in this single-arm, open-label study. The investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

5.1.1. Opioid Toxicity and Withdrawal

5.1.2. Signs and Symptoms of Opioid Toxicity

Acute over dosage with morphine 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.[15,16,17,18] Marked mydriasis rather than miosis may be seen due to severe hypoxia in some overdose situations.[19]

5.1.3. Management of Opioid Toxicity

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 doses of 0.01 mg/kg in pediatric subjects weighing less than 20 kg (or younger than 5 years) and 0.01-0.02 mg/kg for those weighing more than 20 kg (or older than 5 years) up to a total dose of 10 mg.[15,19]

Since the duration of reversal would be expected to be less than the duration of action of morphine in PF-06412528, the subject must be carefully monitored until spontaneous respiration is readily re-established. PF-06412528 will continue to release and add to the morphine 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 morphine 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 PF-06412528 has no role in the treatment of opioid overdose.

5.1.4. 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 dilatation (>4 mm), high pitched crying, restlessness, vomiting, poor feeding, diarrhea, tachypnea, yawning, sneezing, hypertension, and mottling.[20]

5.1.5. Management of Opioid Withdrawal

In general, if significant opioid withdrawal occurs, the subject's symptoms may be medically managed with pediatric doses of midazolam for anxiety and restlessness (250 mcg/kg not to exceed 20 mg),[21] with supplemental doses of morphine sulfate for opioid replacement if necessary, and with pediatric oral doses of ondansetron (4 mg every 8 hours as needed)[22] to control nausea and vomiting. Otherwise, the subject's symptoms can be treated with careful observation and supportive medical care.

5.2. Subject Compliance

Dosing will be recorded in the Daily Diary, transcribed to a case report form (CRF), and discussed at scheduled visits with the caregiver/subject. If a subject's overall 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 after repeated efforts, the investigator should consider discontinuing the subject from the study after confirming the decision with Pfizer.

5.3. Study Drug Supplies

5.3.1. Dosage Form(s) and Packaging

PF-06412528 (morphine sulfate and naltrexone hydrochloride extended release capsules) is a Schedule II (CII) oral dosage form available in the following strengths: 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, and 100 mg/4 mg. For purposes of this study, both a 10 mg/0.4 mg capsule and a 15 mg/0.6 mg capsule will be developed to meet the therapeutic needs of younger (lower weight) children. All PF-06412528 study drug, including the newly developed 10 mg/0.4 mg and 15 mg/0.6 mg capsule strengths, will be supplied by the Sponsor.

PF-06412528 study drug will be packaged and provided for use according to the total daily dose requirements of a subject as listed below:

Morphine Sulfate Total Daily Dose	Dosing Schedule	Capsule (dosage form)	Conversion/ Titration Phase Bottle Fill count (capsules/bottle)	Maintenance Phase Bottle Fill count (capsules/bottle)
10 mg	10 mg QD	CCI	10	20
15 mg	15 mg QD		10	18
20 mg	10 mg BID		20	36
30 mg	15 mg BID		20	36
40 mg	20 mg BID		20	36
60 mg	30 mg BID		20	36
80 mg	2x20 mg BID		40	72
100 mg	50 mg BID		20	36
120 mg	60 mg BID		20	36
160 mg	80 mg BID		20	36
200 mg	100 mg BID		20	36

No other medications, including rescue medications, will be supplied by the Sponsor.

5.3.2. Preparation and Dispensing

Study drug will be shipped to the study center only after receipt of required documents in accordance with applicable regulatory requirements and Sponsor procedures.

Study drug must be dispensed and administered according to the procedures described in the protocol. Only subjects enrolled in the study may receive study drug in accordance with all applicable regulatory requirements. Only authorized study center personnel and the caregiver may supply or administer study drug. 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 study drug inventory at the study centers and will enact resupply of study drug shipments as necessary.

5.4. Administration

PF-06412528 is to be administered with or without food, as per the investigator's Brochure. The bottle label will direct the subject to take either QD or BID depending on the total daily dose requirement for that subject (eg, children of low weight may be assessed to start with the 10 or 15 mg dose QD. Those labels will indicate QD dosing. Dosing strengths greater than 15 mg will indicate BID dosing). When given BID, one dose must be administered in the morning and the second dose is to be administered approximately 12 hours later. Morning doses should be encouraged to be administered daily between 6:00-10:00 AM throughout the study. As a general rule, the initial calculated daily dosage of PF-06412528 should be reduced by 50% and then titrated to achieve a stable dose. When converting to PF-06412528, the investigator should consider the potency, route of administration, and total daily dose of the discontinued opioid(s), the medical status of the subject, the subject's degree of opioid experience and tolerance, the type and severity of chronic pain, and the use of concomitant rescue medications to control the pain. Because

steady-state plasma concentrations are approximated within 24 to 36 hours, PF-06412528 dosage adjustments may be done as frequently as every 1 to 2 days. Study drug will be dispensed to the subject's caregiver only.

When PF-06412528 extended-release capsules are administered whole, the naltrexone remains intact and does not affect the analgesic potential of morphine. However, if the capsule is crushed, chewed or dissolved, the naltrexone component is released, competitively binds at the mu-opioid receptors, thus inhibits the effects of the opioid.

Therefore, PF-06412528 extended-release capsules are to be swallowed whole. The pellets in the capsules are not to be crushed, chewed, or dissolved prior to swallowing.

The co-ingestion of PF-06412528 with alcohol could result in an increase in morphine plasma levels and potentially fatal overdose of morphine. Subjects should not consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on PF-06412528 therapy.

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

As an alternative to taking the capsules whole, and only at the discretion of the investigator, PF-06412528 capsules (pellets) may be sprinkled over applesauce and then swallowed. This method of drug administration is only appropriate for children unable to swallow capsules, but able to reliably swallow the applesauce without chewing it. Capsule shells containing sugar spheres will be provided to assess a subject's swallowing ability on an as needed basis. The investigator also may use the capsule shells to assess a subject's reliability to swallow the applesauce without chewing it in the clinic. When using this method, the caregiver should sprinkle the pellets onto a small amount of applesauce (ie, 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 Drug Administration and Instruction (DAI) guideline.

5.5. Study Drug Storage

According to the investigator's Brochure, all study drug (PF-06412528) should be stored within the range of 59-77°F.

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

Study drug should be stored in its original container and in accordance with the label. See the label for storage conditions of the product.

Storage conditions stated in the SRSD (eg, Investigator's Brochure) will be superseded by the storage conditions stated in the labeling.

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. This should be captured from the time of study drug 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, as applicable, should be regularly inspected to ensure it is maintained in working order.

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. Once an excursion is identified, the study drug must be quarantined and not used until the sponsor provides documentation of permission to use the study drug. It will not be considered a protocol deviation if the sponsor approves the use of the study drug after the temperature excursion. Use of the study drug 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.

Site staff will instruct subjects on the proper storage requirements for take home study drugs.

5.6. Study Drug Accountability

Study drug and bottles 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 unused study drug to the sponsor or sponsor's designee.

Study drug 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 study drug accountability. It is the responsibility of the Sponsor study monitor (or designee) to periodically review study drug accountability records to ensure that FDA regulations and guidelines concerning study drug accountability are being adhered to.

Periodic inventories of study drug during the study and at the end of the study will be performed by the Sponsor study monitor (or designee) and the investigator (or designee). Missing study drug must be recorded on the study drug accountability/return forms along with an explanation of the discrepancy. Missing medication stock must be reported to the Sponsor immediately when discovered. It is essential that all study drug be accounted for. All unused study drug and bottles will be returned to Pfizer or designee, after the proper completion of Drug Enforcement Agency (DEA) 222 forms.

5.6.1. Destruction of Study Drug Supplies

The sponsor or designee will provide guidance on the destruction of unused study drug (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.7. Concomitant Medication(s)

5.7.1. Permitted Medications and Therapies

Permitted medications and therapies during this study will include:

- Acetaminophen and/or NSAID's (as a rescue medication) anytime during the Treatment and Post-Treatment Periods.
- IR morphine as a single ingredient product at usual doses as rescue medication during the Conversion/Titration Phase until a stable dose is achieved. IR morphine for rescue is discouraged during the Maintenance Phase.
- Non-opioid adjunctive analgesics, bowel regimens, and anti-emetics are permitted.
- For any other medications and therapies not listed (eg but not limited to CNS depressants including sedatives, hypnotics, and other tranquilizer-type drugs (eg, benzodiazepines, phenothiazines) the investigator will consult with Pfizer's clinical team because of the risk of hypotension, respiratory depression, and profound sedation or coma.
- Other non-scheduled prescribed medications for treatment of concomitant medical conditions (eg, cancer, arthritis, diabetes).
- Any drug deemed necessary to either treat opioid toxicity (eg, vasopressors, naloxone) or control signs and symptoms of opioid withdrawal (eg, midazolam, ondansetron).
- Stable regimen of prescribed physical therapy, including heat application (at the same intensity and frequency as at study entry).

5.7.2. Prohibited Medications and Therapies

- Opioid analgesics (including tramadol, tapentadol, buprenorphine), except IR morphine as rescue medication during the Conversion/Titration and Maintenance Phases. This includes mixed agonist/antagonist opioid analgesics (eg, pentazocine, butorphanol).
- Monoamine oxidase inhibitors.
- Ethanol in the form of alcoholic beverages (includes medications containing alcohol).

5.8. Rescue Medication

Subjects/caregivers will be required to record use of rescue medication in the diary during the Treatment Period and Post-Treatment Period.

Acetaminophen and/or 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 PF-06412528 to provide pain relief. The use of IR morphine as a rescue medication is permitted during the Conversion/Titration Phase, at the discretion of the investigator, to aid in the conversion.

6. STUDY PROCEDURES

Subjects/caregivers will be asked to complete a diary each day during the Treatment and Post-Treatment Periods of the study.

The investigator (and designee) is 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 are encouraged to 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 parent or 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 Sections 4.1 and 4.2, respectively.
- **Demographics:** Information such as date of birth, race, gender, height, and weight will be collected.
- **Medical History:** Review any significant medical/surgical histories and concurrent illnesses that required or are requiring specialist consultation or treatment.
- **Review Pre-study Opioid Therapy:** Review standard of care opioid therapy and document name, dose, and dosing frequency on the appropriate CRF.
- **Concomitant Medications:** Record all previous (within last 30 days) and concurrent medications (Over-The-Counter or prescribed): Section 5.7.

- **Physical Examination:** See Section 7.2.6.
- **Clinical Laboratory Testing:** Hematology, blood chemistry, and urinalysis (Section 7.2.3).
- **Pregnancy Test:** Conduct serum pregnancy test for all females of childbearing potential (See Section 7.3).
- **Urine Drug Test:** See Section 7.2.7.
- **Electrocardiogram:** See Section 7.2.4.
- **Vital Signs:** Resting blood pressure, pulse rate, and respiration (See Section 7.2.2).
- **Suicide Ideation and Behavior (SIB) Assessment:** C-SSRS (Section 7.4.1):
    - Children's Lifetime/Recent (Ages 7-11) (Version 6/23/10) -Appendix 3.
    - Baseline/Screening (Ages 12-17) (Version 1/14/09) -Appendix 4.
- **COWS:** See Section 7.2.5.
- **Adverse Events:** Reporting of serious adverse events (See Section 7.2.1).
- **Advise** the caregiver that the next visit (Visit 2) is the first dose visit with PF-06412528 and request their child refrain from taking their standard of care opioid on the day of Visit 2. In the event the standard of care opioid has been taken, reschedule the visit for the next day. A telephone call is encouraged the day before Visit 2 to remind the caregiver.

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

Pre-Dose Visit 2 (Day 1)

During this visit (Study Day 1) the following procedures will be followed before the administration of study medication:

- Review any results from laboratory samples (hematology, chemistry, urinalysis, pregnancy tests) that may exclude a subject from participating.
- **Pregnancy Test:** Take a urine sample from all females of childbearing potential.
- **Vital Signs.**

- **SIB Assessment:** C-SSRS (Section 7.4.1):
  - Children's Since Last Visit (Ages 7-11) (Version 6/23/10)-(Appendix 5).
  - Since Last Visit (Ages 12-17) (Version 1/14/09)-(Appendix 6).
- **COWS assessment.**
- **Opioid Therapy Review:** Review standard of care opioid therapy and document name of all opioids, dose, and dosing frequency.
- **Concomitant medications:** Review and document concomitant medication use (name, dose, and frequency).
- **Adverse Event Assessment with focus on serious:** Only pre-dose serious adverse events will be documented.
- **Pain Intensity:** In-clinic assessment.
- **Discontinue previous standard of care opioid therapy as part of dose conversion.**
- **Prescribe Rescue Medication (if needed):** Prescribe rescue medication (acetaminophen and/or NSAID's) to be used during conversion and titration. IR morphine may also be prescribed for rescue, with the intent to limit its use until a stable dose is achieved.
- **Dispense Study Drug:** Dispense appropriate dose of PF-06412528 based on the **Conversion Guide** (as described in Appendix 2).
- **Caregiver(s) Training and Subject Instruction:** Train the caregiver(s) and instruct the subject on study medication 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.
- **Schedule the Visit 3a (Day 7±2 days) visit.**

Visit 3a (Day 7 ±2 Days)

All subjects will have this Day 7 visit, which is designated Visit 3a on the Schedule of Activities.

During this visit, the investigator will review the subject's Daily Diary to assess the subject's pain management to determine whether a stable dose of PF-06412528 has been achieved; ie, a dose that provides adequate analgesia, 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);
  - Concomitant Medication (Diary Review);
  - Study Drug Use (Diary Review);
  - Adverse Events (Diary Review).
- **COWS Assessment.**
- **Concomitant Medication Assessment.**
- **Adverse Event Assessment.**
- **Pregnancy Test:** Take a urine sample from all females of childbearing potential.
- **Vital Signs:** Record blood pressure, pulse rate, and respiration.
- **SIB Assessment:** C-SSRS (Section 7.4.1):
  - Children's Since Last Visit (Ages 7-11) (Version 6/23/10)-(Appendix 5).
  - Since Last Visit (Ages 12-17) (Version 1/14/09)-(Appendix 6).
- **Drug Accountability:** See Section 5.6.
- **Dose Titration:** Adjust PF-06412528 dosage as needed to optimize pain therapy.
- **Prescribe Rescue Medication (if needed):** Prescribe rescue medication (acetaminophen and/or NSAID's) to be used during conversion and titration.
- **Dispense Study Drug** (PF-06412528) to caregiver.

For Converted Subjects: If, at this visit, the subject has been fully discontinued from the standard of care opiate therapy and successfully titrated to a stable dose of PF-06412528 and with infrequent use of IR morphine for rescue the subject may be scheduled for the next visit, which will be Visit 4 (Schedule of Activities). It is at this visit (Visit 3a) the subject enters the Maintenance Phase of the Treatment Period.

For Non-Converted Subjects: If, at this visit, the subject **has not** achieved a stable dose of PF-06412528, this subject will remain in the Conversion/Titration Phase, therefore:

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 this visit, the subject has been fully discontinued from the standard of care opiate therapy and successfully titrated to a stable dose of PF-06412528 and with infrequent use of IR morphine for rescue the subject may be scheduled for the next visit, which will be Visit 4 (Schedule of Activities). It is at this visit (Visit 3b) the subject enters the Maintenance Phase of the Treatment Period.

For Non-Converted Subjects: If, at this visit, the subject **has not** achieved a stable dose of PF-06412528, this subject will remain in the Conversion/Titration Phase, therefore:

- **Schedule the Visit 3c (Day 21 ±2) visit.**

Visit 3c (Day 21 ±2 days)

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

For Converted Subjects: If, at this visit, the subject has been fully discontinued from the standard of care opiate therapy and successfully titrated to a stable dose of PF-06412528 and with infrequent use of IR morphine for rescue the subject may be scheduled for the next visit, which will be Visit 4 (Schedule of Activities). It is at this visit (Visit 3c) subject enters the Maintenance Phase of the Treatment Period.

For Non-Converted Subjects: If, at this visit, the subject **has not** achieved a stable dose of PF-06412528, the subject will remain in the Conversion/Titration Phase, therefore:

- **Schedule the Visit 3d (Day 28 ±2 days) visit.**

Visit 3d (Day 28 ±2 days)

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

For Converted Subjects: If, at this visit, the subject has been fully discontinued from the standard of care opiate therapy and successfully titrated to a stable dose of PF-06412528 and with infrequent use of IR morphine for rescue the subject may be scheduled for the next visit, which will be Visit 4 (Schedule of Activities). It is at this visit (Visit 3d) subject enters the Maintenance Phase of the Treatment Period.

For Non-Converted Subjects: If, at this visit, the subject **has not** achieved a stable dose of PF-06412528, the subject will be discontinued from treatment. PF-06412528 will be discontinued and if needed, converted to a standard of care analgesic therapy at the investigator's discretion.

- **Schedule the Visit 6/Early Termination Visit: See Section 6.3.**

- **Schedule the Post Treatment/End of Study (Visit 7): See Section 6.4.**

6.2.2. Maintenance Phase

Once the investigator has determined that the subject has achieved a stable dose of PF-06412528, the subject will enter the Maintenance Phase of the Treatment Period and scheduled to return in two weeks for Visit 4. In the event a subject prematurely withdraws before Visit 4, perform the Visit 6/ET procedures a soon as possible.

Visit 4

Perform the following assessments:

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

- **Obtain Plasma Samples:** Obtain 2 separate 6 mL blood samples for measurement of the concentration of morphine and metabolites in plasma and naltrexone and 6-β-naltrexone in plasma, with at least 2 hours separating the 1st and 2nd samples.

  Record the following items on the appropriate CRF:

  - The exact dosing date and clock times of the morning dose and previous 3 doses of PF-06412528, and

  - The exact clock time of the blood draw for the 2 samples.

Visit 5

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

Visit 6/Early Termination

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

- Physical examination.

- Serum pregnancy test.

- Clinical Laboratory Test (Hematology, blood chemistry and urinalysis): See Section 7.2.3.

- Follow the same procedures and assessments as described at Visit 3a, (except do not perform the urine pregnancy test, instead a serum pregnancy test should be performed at this visit): See Schedule of Activity and Section 7.3.

- 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 time for the morning and previous 3 doses of PF-06412528, and
  - The exact clock time of the blood draw for the 2 samples.
- Subjects who discontinue early from the study as well as subjects who complete 2 weeks of PF-06412528 during the Maintenance Phase and have their last dose of PF-06412528 at Visit 4 will complete the Visit 6/Early Termination procedures without the need to return for the Post Treatment/End of Study Visit.
- Schedule Post Treatment/End of Study Visit, if required.

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 the PF-06412528 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 6/Early Termination (see Section 6.2.2).

6.4. Post Treatment/End of Study (EOS) Visit 7

Approximately 1 week after discontinuing PF-06412528 and initiating dose conversion back to the subject's standard of care therapy, subjects will undergo the Post-Treatment/End of Study procedures, which will consist of an assessment of any **AEs** since the previous visit and the **suicidality assessment**.

The following procedures will include:

- **SIB Assessment: C-SSRS (Section 7.4).**
- **AE assessment.**

6.5. Subject Withdrawal

Withdrawal of consent: caregivers/subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when the caregiver/subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Caregiver/subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study drug or also from study procedures and/or post treatment study follow-up, and entered on the appropriate

CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety 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.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. 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 return all unused study drug, request the subject to return for a final visit, if applicable, and follow-up with the subject 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/suicidality).

Subjects who do not reach a stable dose by Visit 4 (Day 28) will be discontinued from the study. Subjects who have illicit substances at Screening on the UDT will be discontinued from the study, unless supported by prescription for medicinal use. 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 the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

In the event of clinically important treatment-emergent suicidal ideation or suicidal behavior, the subject will be withdrawn from the study and will receive the appropriate medical care, which may include medication. 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 mental health provider as part of the psychiatric evaluation and assessment of subject safety. Refer to Section 7, 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)

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

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 6 visit. The following attempts must be made in the order listed below:

1. 3 documented* attempts via telephone; then

2. 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 for Pain, Adverse Events

If at any time pain increases during the Treatment Period, rescue medication therapy is preferred, which includes IR morphine as necessary. For unscheduled visits due to an increase in pain where up-titration is necessary, record at a minimum, the Numeric Rating Scale (NRS) pain and COWS scores on the appropriate 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 6/ET procedures to be performed (Schedule of

Activities). An unscheduled visit due to a combination of an AE and an increase in pain requires the Visit 6 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 which he/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 NRS ranging from zero (no pain) to 10 (worst possible pain) captured on the diary (Appendix 7). A subject will rate their average pain intensity during the past 24 hours by choosing the appropriate number from 0 to 10 as shown below. The subject will conduct the self-assessment daily with the caregiver(s) in the evening prior to bedtime and recorded 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 and will not be documented. Pain Intensity will also be completed at the in-clinic visits during the Treatment and Post-Treatment Periods. Only the in-clinic visit pain assessments will be documented for analysis.

Select the number that best describes your average 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

7.1.2. Rescue Medication Use

The use of Rescue Medication will be recorded in the diary during the Treatment and Post-Treatment Periods.

The administration of acetaminophen and/or NSAID's administered during the study is recorded by the caregiver(s), but is not to be more than required by label and at the direction of the investigator.

7.2. Safety Assessments

7.2.1. Adverse Events

7.2.1.1. Recording of Adverse Events by Investigator

The investigator is responsible for the detection and documentation of all events meeting the definition of an AE or serious adverse event (SAE). All AEs and SAEs will be recorded in the source documents. All AEs will be entered on the appropriate CRF page from the time of dosing until completion of the End of Study requirements. All SAEs will be recorded on the CRF from the time written informed consent is given until 28 days after the last dose of study drug is administered. Information collected will include the nature of the event, as well as its date and time of onset, intensity, duration, causality, and outcome. Even if the investigator regards the AE as not reasonably attributable to study drug, the event must be recorded in the source documentation including the CRF.

7.2.1.2. Recording of Adverse Events Using a Home Diary

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

7.2.2. Vital Signs

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

7.2.3. Clinical Laboratory Tests

The hematology, clinical chemistry, and urinalysis tests presented in Table 1 are performed at designated study visits as outlined in the Schedule of Activities.

Table 1. Clinical Laboratory Tests

Serum Chemistry	
Alanine aminotransferase (ALT; serum glutamate pyruvate transaminase)	Chloride
Albumin	Serum creatinine
Alkaline phosphatase	Creatine phosphokinase
Aspartate aminotransferase (AST; serum glutamic oxaloacetic transaminase)	Glucose
Bicarbonate	Phosphorus
Bilirubin (total)	Potassium
Blood urea nitrogen	Protein (total)
Calcium	Sodium

Serum Chemistry	
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)
Other	
Routine urinalysis (dip-stick unless otherwise indicated)	

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. An abnormal, clinically significant finding at screen will be cause to not enroll the subject. 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 opiate withdrawal.[23]

A subject experiencing a COWS score ≥13 is 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.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

Height and weight is measured only at Visit 1 of the Screening Period.

7.2.7. Urine Drug Test

A urine drug sample is collected at Screening, as outlined in the Schedule of Activities, for the purpose of mainly detecting illicit drug substances. Certain positive test results may be acceptable providing documentation is confirmed by the investigator. An opioid finding at the Screening visit is an expected result due to a subject's standard of care therapy not being discontinued at Screen or washed out by the Baseline visit. Illicit drugs found during these tests will disqualify the subject from entering the study.

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

- Opioids (ie, codeine, morphine, hydrocodone, hydromorphone, dihydromorphone, oxycodone);
- Amphetamines (including methamphetamine and ecstasy);
- Phencyclidine;
- Cocaine;
- Tetrahydrocannabinol (marijuana);
- Methadone.

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 and Visit 6/ET, and a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at all other study visits (ie, Visits 2-5), including unscheduled visits. A negative pregnancy result is required before the subject may receive the study drug. Pregnancy tests will also be done whenever one menstrual cycle is missed during the treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study to confirm the subject has not become pregnant during the study. In the case of a positive human chorionic gonadotropin test, the subject will be withdrawn from study medication but may remain in the study. Pregnancy tests may also be repeated as per request of IRB/Ethics Committees (EC) or if required by local regulations.

7.4. Assessment of Suicidal Ideation and Behavior

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

Suicide ideation and behaviors will be evaluated at all scheduled visits from Screening (Visit 1) through End of Study (Visit 7). The age-appropriate scale must be utilized based upon the subject's age at the Screen (Visit 1) visit.

For subjects who will be ages 7-11:

- The Children's Lifetime/Recent (Version 6/23/10) (Appendix 3) of the C-SSRS should be completed at the Screening Visit (Visit 1). Please note the Lifetime/Recent scale refers to the subject's lifetime experience. At all study visits following the Screening Visit, the Children's Since Last Visit (Version 6/23/10) (Appendix 5) of the C-SSRS should be utilized, even if the child has their 12th birthday during the study. The Since Last Visit version refers to the subject's experience since their last visit.

For subjects who will be ages 12-17:

- The Baseline/Screening (Version 1/14/09) (Appendix 4) of the C-SSRS should be completed at the Screening Visit (Visit 1). Please note the Screening scale refers to the subject's lifetime experience. At all study visits following Visit 1, the Since Last Visit (Version 1/14/09) (Appendix 6) of the C-SSRS should be utilized. The Since Last Visit version refers to the subject's experience since their 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 discontinued 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 the following child and adolescent mental health provider (MHP): In the United States: 1) Child and Adolescent Psychiatrists (board certified or board eligible), 2) psychiatrists who have training and experience in the diagnosis and treatment of psychiatric disorders in the pediatric population, or 3) Psy.D. or Ph.D. level Clinical Psychologists, licensed Master's level Clinical Social Workers (MSW), or licensed psychiatric Nurse Practitioners (PNP) who have training and experience in the diagnosis and treatment of psychiatric disorders in the pediatric population.

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 withdrawn from the study and will receive the appropriate medical care. Refer to Section 6.5, Subject Withdrawal.

7.5. Pharmacokinetic Evaluation

7.5.1. Blood Sample Collection and Handling

During Visit 4, a total of two 6 mL (2×6 mL) PK samples of blood will be taken at least two hours apart for the purpose of quantifying the concentrations of morphine, M3G, M6G, naltrexone, and 6-β-naltrexol in plasma. PK samples will be collected at Visit 6 or at Early Termination if they are not collected at Visit 4. The clock time of the first PK sample will be documented (and noted relative to the clock time of the morning dose of PF-06412528) on the CRF. The second PK 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 3 doses are also to be recorded on the appropriate CRF.

Plasma samples received by the bioanalytical laboratory will be assayed for either morphine and morphine metabolites (MG3, MG6) or naltrexone and 6-β-naltrexol using a validated analytical method 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.

7.5.2. Plasma Sample Shipment to Bioanalytical Laboratory

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

7.6. Blood Volume

Total blood sampling volume for the individual subjects is approximately 36 mL.

Blood Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening	Treatment Period	End of Study	
Safety Labs	6	1		1	12
Pregnancy*	6	1		1	12
PK	6		6 mLX 2		12
TOTAL					36

This total volume does not include discarded blood from pre-draws used to remove fluid from flushed catheters.
* Includes only females of child-bearing age who are sexually active.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the study drug(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 an 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 non-serious adverse event 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 trial.

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 study drug, through and including 28 calendar days after the last administration of the study drug. Serious adverse events 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 serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.

- AEs (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of study treatment through last subject 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 drug, 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 study drug;
- 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 AE(s) 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 withdrawal 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

An SAE 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.

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. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) levels concurrent with abnormal elevations in total bilirubin 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 ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 X ULN or not available.

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

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

    Concurrent with

    - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased from baseline by an amount of at least 1 X ULN **or** if the value reaches ≥3 X 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 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 subject, 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 to 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 work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- 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;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive 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 case report forms (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 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 non-serious); 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 study drug 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 study drug caused the event, then the event will be handled as "related to study drug" 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 study drug", this should be clearly documented on study records.

In addition, if the investigator determines 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 investigational products study treatment 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 being exposed (eg, because of treatment or environmental exposure) to the study drug; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the study drug.

   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 study drug 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 study drug, the investigator must submit this information to the Pfizer Drug Safety Unit on a SAE report form and 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 pre-procedure 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, 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 study drug.

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 safety within 24 hours of 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 study master file.

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

Withdrawal due to AE 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 due to an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject/parent/legal guardian. In addition, each study subject/parent/legal guardian will be questioned about AEs.

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 timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and 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. Non-serious 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 Reporting Requirements to Regulatory Authorities

Adverse event 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. Sample Size Determination

The study plans to enroll approximately 140 subjects for the purpose of establishing a safety database, with at least 100 subjects exposed to at least 2 weeks of the Maintenance Phase with neither age group exceeding a 3:1 margin compared to the other age group (7-11 years old and 12-17 years old).

CCI [redacted]

CCI [redacted]

9.2. Efficacy Analysis

Analgesic effect analyses will be performed using all available in-clinic pain intensity data from the safety population (see 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 will be defined as all subjects with at least 1 plasma concentration measurement in this study. The PK analysis population will be defined as all pediatric subjects who have usable PK data (ie, data for which the relationship between the time of dose time of sampling can be determined) and are included in the estimates of the primary pharmacokinetic parameters of interest.

9.3.2. Pharmacokinetic Endpoints

Primary PK endpoints will include estimates of morphine $C_{ss,av}$ and CL/F. Secondary PK endpoints will include Vz/F of morphine, data permitting. The exposure levels of the metabolites of morphine M3G and M6G, naltrexone, 6-β-naltrexol following multiple dose treatment with PF-06412528. Graphical representations and regression analyses may be used to characterize the dose-exposure relationships for morphine, naltrexone, and 6-β-naltrexol (data permitting).

9.3.3. Pharmacokinetic Analysis

Given the expected very low fluctuation in steady-state morphine concentrations following PF-06412528 BID dosing in children based on PF-06412528 study ALO-KNT-202 in adults, the concentrations observed during the maintenance phase will be used as an estimate of $C_{ss,av}$ of morphine and its metabolites (data permitting) in pediatric subjects. The CL/F of morphine will be estimated using a ratio of the daily dosing rate of PF-06412528 and the estimates of morphine $C_{ss,av}$ in the Maintenance Phase. The concentration-time dataset will be analyzed to obtain estimates for Vz/F of morphine in pediatric subjects, data permitting. Covariates of interest (PF-06412528 dosage, age, body weight, gender, concomitant medications etc) will be assessed for their ability to account for the observed variability in morphine $C_{ss,av}$.

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

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 PF-06412528.

Safety data will be summarized for the Safety population.

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 PF-06412528 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 withdrawal 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 including changes from Screening 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.

9.5. Interim Analysis

No interim analysis is planned for this study.

9.6. Data Monitoring Committee

This study will use an 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 is 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 IRB/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 is true. Any corrections to entries made in the CRFs, 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 investigator’s 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 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, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), 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 to 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 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/IEC 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 [International Committee on Harmonization (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

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

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 the 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 subjects’ personal data consistent with applicable privacy laws.

The informed consent document 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/her legal representative, 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 legal representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Subject Recruitment

Advertisements approved by ethics committees 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 which might influence the evaluation of the benefits and risks of the study treatment, 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 in all Participating Countries

End of Trial in all participating countries is defined as Last Subject Last Visit and meeting all of the End of Study requirements.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06412528 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), www.pfizer.com, and/or the European Clinical Trials Database (EudraCT), 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 subjects 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.

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
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice-a-day
BPCA	Best Pharmaceuticals for Children Act
CL/F	apparent oral clearance
Cmax	peak concentration
CNS	Central Nervous System
COWS	Clinical Opiate Withdrawal Scale
CRF	case report form
CSA	clinical study agreement
Css, av	average concentration at steady-state
Css, min	minimum concentration at steady-state
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
DAI	dosage and administration instructions
DEA	Drug Enforcement Agency
EC	ethics committee
ECG	electrocardiogram
EDP	exposure during pregnancy
ET	early termination
FDA	Food and Drug Administration (United States)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HCl	hydrochloride
ICH	International Conference on Harmonisation
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IVR	interactive voice response
LFT	liver function test
M3G	morphine 3 glucuronide
M6G	morphine 6 glucuronide
medDRA	Medical Dictionary and Regulatory Activities
MHP	mental health provider
mL	milliliter
NRS	Numeric Rating Scale

Abbreviation	Term
NSAID	non-steroidal anti-inflammatory drug
PASS	Post-Authorization Safety Study
PK	pharmacokinetic
PREA	Pediatric Research Equity Act
QD	once-a-day
SAE	serious adverse event
SIB	suicidal ideation and behavior
SOC	standard of care
SRSD	single reference safety document
UDT	urine drug test
ULN	upper limit of normal
US	United States
Vz/F	apparent volume of distribution

Appendix 2. Conversion Guide

PF-06412528 CONVERSION GUIDE

This conversion guide summarizes published relative potency data to help healthcare professionals convert treatment regimens for subjects with moderate to severe chronic pain to an approximate daily equianalgesic dose of PF-06412528. The conversion ratios in this guide are for converting from other opioids to PF-06412528 only. Only oral and transdermal (not rectal) conversion information is provided. These conversion ratios are only approximate and are not to be used in the reverse.

The tables included in this booklet should be considered for guidance only, and the actual dose of any opioid product should be based on clinical judgment and adjusted on an individual basis.

IMPORTANT INFORMATION ABOUT THIS GUIDE:

Due to incomplete cross-tolerance when converting from a non-morphine analgesic to PF-06412528, 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 morphine requirement and provide rescue medication rather than to overestimate and manage an adverse event.[1]

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.

HOW TO CONVERT FROM TRANSDERMAL FENTANYL TO PF-06412528:

1. Determine the total daily dose of transdermal fentanyl.

   Note that fentanyl is approximately 50 to 150 times more potent than morphine.[2]

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).[3]

3. Refer to the analgesic table below to find the equianalgesic dose of PF-06412528. 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 PF-06412528, either as a single dose q24h or in 2 divided doses q12h. PF-06412528 should not be given more frequently than every 12 hours.

CONVERTING FROM TRANSDERMAL FENTANYL TO PF-06412528:[2,3,4,5,6]

Transdermal fentanyl daily dose[a]	Equianalgesic morphine daily dose (mg)	Suggested equianalgesic dose of PF-06412528 administered q24h or in 2 divided doses q12h (mg)	Suggested starting dose of PF-06412528 at ≈50% reduction based on existing capsule strengths (mg)[b]
12.5 mcg/h=300 mcg/day	30	30	15 QD
25 mcg/h=600 mcg/day	60	60	15 BID
50 mcg/h=1200 mcg/day	120	120	30 BID
75 mcg/h=1800 mcg/day	180	180	2X20 BID
100 mcg/h=2400 mcg/day	240	240	60 BID

a Calculate the total daily dose of transdermal fentanyl.

b It is likely that rescue medication may be needed for breakthrough pain until the dose of PF-06412528 can be titrated to the effective daily dose, thus ensuring a smooth transition. After patch removal, 17 or more hours are required for a 50% decrease in serum fentanyl concentration in healthy individuals.[3]

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.

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.

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 HYDROCODONE TO PF-06412528:

1. Determine the total daily dose of hydrocodone.
2. Calculate the conversion of the total daily dose of the current hydrocodone therapy into the equianalgesic dose of morphine using the appropriate ratio (based on an approximate equianalgesic ratio of 1:1).[7]
3. Refer to the analgesic table below to find the equianalgesic dose of PF-06412528. 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 PF-06412528, either as a single dose q24h or in 2 divided doses q12h. PF-06412528 should not be given more frequently than every 12 hours.

CONVERTING FROM HYDROCODONE TO PF-06412528:

Hydrocodone daily dose (mg)[a]	Equianalgesic morphine daily dose (mg)	Suggested equianalgesic dose of PF-06412528 administered q24h or in 2 divided doses q12h (mg)	Suggested starting dose of PF-06412528 at ≈50% reduction based on existing capsule strengths (mg) [b]
20	20	20	10 QD
30	30	30	15 QD
40	40	40	10 BID
60	60	60	15 BID
80	80	80	20 BID

a Calculate the total daily dose of hydrocodone. At lower doses of hydrocodone, it may be necessary to start with the lowest strength of PF-06412528.
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.

b It is likely that rescue medication may be needed for breakthrough pain until the dose of PF-06412528 can be titrated to the effective daily dose, thus ensuring a smooth transition.

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.

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 PF-06412528:

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).[7]
3. Refer to the analgesic table below to find the equianalgesic dose of PF-06412528. 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 PF-06412528, either as a single dose q24h or in 2 divided doses q12h. PF-06412528 should not be given more frequently than every 12 hours.

CONVERTING FROM HYDROMORPHONE TO PF-06412528[7-9]:

Hydromorphone daily dose (mg)[a]	Equianalgesic morphine dose (mg)	Suggested equianalgesic dose of PF-06412528 administered q24h or in 2 divided doses q12h (mg)	Suggested starting dose of PF-06412528 at ≈50% reduction based on existing capsule strengths (mg)[b]
6	24	20	10 QD
8	32	30	15 QD
12	48	50	10 BID
16	64	60	15 BID
20	80	80	20 BID
24	96	100	30 BID

a Calculate the total daily dose of hydromorphone.
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.

b It is likely that rescue medication may be needed for breakthrough pain until the dose of PF-06412528 can be titrated to the effective daily dose, thus ensuring a smooth transition.

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.

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 PF-06412528:

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).[9,10]
3. Refer to the analgesic table below to find the equianalgesic dose of PF-06412528. 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 PF-06412528, either as a single dose q24h or in 2 divided doses q12h. PF-06412528 should not be given more frequently than every 12 hours.

CONVERTING FROM METHADONE TO PF-06412528:[2,9,10,11,12]

Methadone daily dose (mg)[a]	Equianalgesic morphine dose (mg)	Suggested equianalgesic dose of PF-06412528 administered q24h or in 2 divided doses q12h (mg)	Suggested starting dose of PF-06412528 at ≈50% reduction based on existing capsule strengths (mg)[b]
20	60	60	15 BID
30	90	90	20 BID
40	120	120	30 BID
50	150	150	2X20 BID
60	180	180	50 BID
80	240	240	60 BID
100	300	300	80 BID

a. Calculate the total daily dose of methadone.

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.

b. It is likely that rescue medication may be needed for breakthrough pain until the dose of PF-06412528 can be titrated to the effective daily dose, thus ensuring a smooth transition.

Data on the equianalgesic dose of methadone compared with morphine are inconclusive. Conversion ratios in many commonly used equianalgesic dosing tables do not apply in the setting of repeated methadone dosing. Although with single-dose administration, the onset and duration of analgesic action as well as the analgesic potency of methadone and morphine are similar, methadone's potency increases over time with repeated dosing.[2,9]

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.

OTHER 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 OTHER MORPHINE PRODUCTS TO PF-06412528:

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, using the appropriate ratio (1:1).
3. Refer to the specific analgesic table below to find an equianalgesic dose of PF-06412528.
4. Administer the calculated dose in the most convenient dosing strength of PF-06412528, either as a single dose q24h or in 2 divided doses q12h. PF-06412528 should not be given more frequently than every 12 hours.

CONVERTING FROM OTHER MORPHINE PRODUCTS TO PF-06412528:

Morphine daily oral dose (mg)[a]	Equianalgesic morphine oral dose (mg)	Suggested equianalgesic dose of PF-06412528 administered q24h or in 2 divided doses q12h (mg)	Suggested starting dose of PF-06412528 at ≈50% reduction based on existing capsule strengths (mg) [b]
30	30	30	15 QD
60	60	60	15 BID
90	90	90	20 BID
100	100	100	30 BID
200	200	200	50 BID

a Calculate the total daily morphine dose. This amount can be given as PF-06412528 in a single daily q24h dose or in 2 divided doses q12h.

b Consider giving the subject rescue medication to make up the difference (if the starting dose is less than an equianalgesic dose) until the dose of PF-06412528 is titrated to the effective daily dose.

To convert from parenteral morphine, a dose of oral morphine 3 times the daily parenteral morphine requirement may be sufficient in chronic use settings.

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 OXYCODONE TO PF-06412528:

1. Determine the total daily dose of oxycodone.
2. Calculate the conversion of the total daily dose of the current oxycodone therapy into the equianalgesic dose of morphine, using the appropriate ratio (based on an approximate equianalgesic ratio of 1:1.5).[7]

3. Refer to the analgesic table below to find the equianalgesic dose of PF-06412528. 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 PF-06412528, either as a single dose q24h or in 2 divided doses q12h. PF-06412528 should not be given more frequently than every 12 hours.

CONVERTING FROM OXYCODONE TO PF-06412528:[7,13]

Oxycodone daily dose (mg)[a]	Equianalgesic daily morphine dose (mg)	Suggested equianalgesic dose of PF-06412528 administered q24h or in 2 divided doses q12h (mg)	Suggested starting dose of PF-06412528 at ≈50% reduction based on existing capsule strengths (mg)[b]
20	30	30	15 QD
30	45	40	10 BID
40	60	60	15 BID
60	90	90	20 BID
80	120	120	30 BID
100	150	150	2X20 BID

a Calculate the total daily dose of oxycodone.
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.

b It is likely that some rescue medication may be needed for breakthrough pain until the dose of PF-06412528 can be titrated to the effective daily dose, thus ensuring a smooth transition.

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 IR morphine.

OXYMORPHONE PRODUCTS:

- Opana® (oxymorphone hydrochloride) Tablets, 5 mg, 10 mg; Opana ER (oxymorphone hydrochloride) Extended-Release Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg.

HOW TO CONVERT FROM OXYMORPHONE TO PF-06412528:

1. Determine the total daily dose of oxymorphone.
2. Calculate the conversion of the total daily dose of the current oxymorphone therapy into the equianalgesic dose of morphine, using the appropriate ratio (based on an approximate equianalgesic ratio of 1:2-10).[9,14,15]
3. Refer to the analgesic table below to find the equianalgesic dose of PF-06412528. 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 PF-06412528, either as a single dose q24h or in 2 divided doses q12h. PF-06412528 should not be given more frequently than every 12 hours.

CONVERTING FROM OXYMORPHONE TO PF-06412528:[9,14,15]

Oxymorphone daily dose (mg)[a]	Equianalgesic morphine dose (mg)	Suggested equianalgesic dose of PF-06412528 administered q24h or in 2 divided doses q12h (mg)[b]	Suggested starting dose of PF-06412528 at ≈50% reduction based on existing capsule strengths (mg)[b]
10	20	20	10 QD
20	40	40	10 BID
40	80	80	20 BID

a Calculate the daily dose of oxymorphone.
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.

b It is likely that rescue medication may be needed for breakthrough pain until the dose of PF-06412528 can be titrated to the effective daily dose, thus ensuring a smooth transition.

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.

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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 1/14/09)-Age12-17

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 Numeric Rating Scale (NRS-Pain)

Question:

Select the number that best describes your average 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.