Official Title: A Study to Characterize the Time Course of Reversal of Opioid (Fentanyl)-Induced Respiratory Depression Following Administration of Nalmefene Autoinjector 1.5 mg (0.94% $MgCl_2$) Intramuscular·and Narcan® 4 mg Intranasal in Healthy Subjects

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Protocol Number:	NAL1004
Title:	A Study to Characterize the Time Course of Reversal of Opioid (Fentanyl)-Induced Respiratory Depression Following Administration of Nalmefene Autoinjector 1.5 mg (0.94% $MgCl_2$) Intramuscular and Narcan® 4 mg Intranasal in Healthy Subjects
Sponsor:	Purdue Pharma, LP One Stamford Forum Stamford, CT 06901-3431 USA
Test Drugs:	Fentanyl, Nalmefene Hydrochloride, Naloxone Hydrochloride
Phase:	Phase 1
Approval Date:	October 12, 2022
Amendment No:	2
GCP Statement:	This study is to be performed in compliance with ICH and applicable Good Clinical Practices (GCPs) and federal and local regulations.
Confidentiality:	This document is confidential. It contains proprietary information of Purdue Pharma, LP. Any viewing or disclosure of such information that is not authorized in writing by the sponsor (or designee) is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Study to Characterize the Time Course of Reversal of Opioid (Fentanyl)-Induced Respiratory Depression Following Administration of Nalmefene Autoinjector 1.5 mg (0.94% $MgCl_2$) Intramuscular and Narcan® 4 mg Intranasal in Healthy Subjects

Brief Title:

Pharmacodynamic Evaluation of Intramuscular Nalmefene Autoinjector 1.5 mg compared to Intranasal Narcan 4 mg

Rationale:

There are ethical challenges associated with conducting an efficacy study in the setting of opioid overdose using Nalmefene when life-saving, already-approved products are available, or to intentionally overdose subjects with opioids in a controlled setting in order to describe the onset of action and safety of Nalmefene.

In order to characterize the reversal onset of nalmefene, a pharmacodynamic evaluation of Nalmefene Autoinjector 1.5 mg (intramuscular) compared to Narcan 4mg (intranasal) has been designed.

Purdue has completed the conduct of a non-IND methods clinical study, NAL9001, to develop and refine pharmacodynamic (PD) methods of assessing respiratory depression and other effects caused by an opioid (fentanyl) and clinical study NAL1003 which utilized this opioid (fentanyl)-induced respiratory depression model.

In NAL1003, the onset and time course of nalmefene or naloxone antagonism of opioid agonist (fentanyl) induced respiratory effects was characterized. Nalmefene 1 mg, IM, anterolateral thigh; Naloxone 2 mg, IM, anterolateral thigh; and Narcan 4 mg, IN were administered following OIRD. Fentanyl was administered as a 3 step infusion, with a maximum total duration of 230 minutes to maintain steady state fentanyl concentrations once opioid-induced respiratory depression (OIRD) was reached with the 1st infusion. The duration of the fentanyl infusions was individualized (i.e., based on individual subjects rather than the entire cohort of subjects), based on ongoing assessments of minute ventilation measured to determine opioid effects and OIRD. Fentanyl, when co-administered with and without Nalmefene or Naloxone standard of care treatment, was found to be safe as employed in this model of OIRD. Taking into consideration the potency of nalmefene, the pharmacodynamic data suggest that Nalmefene 1 mg IM produced time to onset of reversal in minute ventilation comparable or better than Naloxone standard of care treatments.

This study will evaluate opioid-induced respiratory depression (OIRD) following the administration of fentanyl and after coadministration of nalmefene or naloxone, using noninvasive respiratory volume monitoring (eg, ExSpiron) to determine minute ventilation (the product of tidal volume x respiratory rate), and a transcutaneous CO_2 monitor. Subjects will be

monitored continuously for oxygen saturation and may receive supplemental oxygen by mask to enhance safety.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the change in minute ventilation at 5 minutes of intramuscular nalmefene and intranasal naloxone reversal from the opioid induced nadir	• Change in minute ventilation 5 minutes from opioid induced nadir
Secondary	
• To assess the time course of changes in minute ventilation of intramuscular nalmefene and intranasal naloxone reversal from the opioid induced nadir	• Change in minute ventilation at 2.5, 10, 15, 20 and 90 minutes from opioid induced nadir • Maximum change in minute ventilation 90 minutes from opioid induced nadir • Time to maximum change in minute ventilation 90 minutes from opioid induced nadir
• To evaluate the pharmacokinetics of nalmefene and naloxone following various routes of administration	• Plasma concentrations of nalmefene and naloxone will be analyzed to determine the following PK parameters for each treatment: $AUC_{0\text{-}2.5}$, $AUC_{0\text{-}5}$, $AUC_{0\text{-}10}$, $AUC_{0\text{-}15}$, $AUC_{0\text{-}20}$, AUC_t, AUC_{inf}, C_{max}, T_{max}, T_{lag}, $T_{1/2}$
• To assess the safety and tolerability of fentanyl when co-administered with and without nalmefene or naloxone	• Safety will be assessed using recorded AEs, clinical laboratory test results, vital signs, SpO2, physical examinations, and conventional 12-lead ECGs and local tolerability
Exploratory	
• To characterize the time course (Magnitude of change in minute ventilation) of intramuscular nalmefene and intranasal naloxone reversal from the opioid induced nadir	• Time to Onset (TTO) - Thresholds (X%) of reversal defined as X% of baseline reversal and calculated as X %) * (Baseline – OIRD) + OIRD, where X are 25, 33, 50, 67, 75, 90, and 100. Each Threshold % provides varying degrees of reversal.

Overall Design:

This will be a 2 part study. Part 1 is a Qualification Phase prior to Part 2 which will be conducted to identify subjects eligible to participate in the Treatment Phase. This will be based upon satisfying specified qualification criteria following completion of procedures and/or study drug administrations. Qualification may not be required if a subject has participated in previously conducted Clinical Studies (NAL9001, NAL1002, and NAL1003). Each Qualification cohort will have a screening, treatment, EOS and Follow-up. The qualification treatment phase will consist of 1 period and evaluate the pharmacodynamics (minute ventilation) of OIRD. Qualification may be repeated if a subject has results that are uncertain regarding his or her suitability for Treatment (e.g., because of high variability or interference in minute ventilation, questionable equipment function/optimization, and/or other issues that render the data suboptimal).

Part 2 will be a single-center, randomized, 4 period crossover, 2 treatment replicate study to evaluate the pharmacodynamic effects (change in minute ventilation from opioid induced nadir (OIRD)) of nalmefene (1.5 mg) when given as an autoinjector intramuscularly (IM; into the thigh) compared to naloxone (Narcan 4 mg) when given intranasally (IN; into the nose) to reverse opioid (fentanyl) -induced respiratory depression (OIRD) in healthy subjects with prior opioid exposure. The Treatment Phase will have a screening, treatment, EOS and Follow-up.

Brief Summary:

This study is to determine the pharmacodynamics (change in minute ventilation) of nalmefene when given as an autoinjector intramuscularly (IM; into the thigh) compared to naloxone when given intranasally (IN; into the nose) to healthy subjects with prior opioid exposure under steady state fentanyl concentrations (opioid agonism).

Study details include:

- The study design graphic depicts the duration of each part.
- Part 1: Qualification Phase
    - Total study duration: up to approximately 40 days.
    - Subjects will be confined to the unit beginning the day prior to study drug administration (Check-in) in period 1 until End of Study (EOS) (or upon early discontinuation). Subjects who are ready for discharge on the same day as fentanyl administration should be required to have a ride home.
- Part 2: Treatment Phase
    - Total study duration: up to approximately 78 days.
    - Subjects will be confined to the unit beginning the day prior to study drug administration (Check-in) in period 1 until End of Study (EOS) (or upon early discontinuation). Subjects who are ready for discharge on the same day as fentanyl administration should be required to have a ride home.

Number of Participants:

Part 1: A sufficient number of subjects will be screened and entered into Part 1 to provide the number of subjects required in Part 2.

Part 2: A total of up to 22 subjects will be randomized to complete approximately 20.

In a non-inferiority test on MV at 5min from a 4 period, 2 treatment replicate cross-over design, a total sample size of 20 would achieve >90% power at a 2.5% significance level (1-sided) when the true difference between the means is 0.8L/min, the non-inferiority margin is -0.5L/min, and the within-subject standard deviation is 1.2L/min.

In a superiority test on MV at 5min from a 4 period, 2 treatment replicate cross-over design, a total sample size of 20 would achieve 83% power at a 2.5% significance level (1-sided) when the true difference between the means is 0.8L/min and the within-subject standard deviation is 1.2L/min.

The planned sample size is adequate for sequential testing of non-inferiority followed by superiority.

Study Population:

Part 1: Healthy male and female subjects with prior opioid exposure aged 18 to 55 years, inclusive, with no clinically significant medical history, who are deemed by the investigator suitable to take part in this clinical study.

Part 2: Qualified healthy male and female subjects with prior opioid exposure aged 18 to 55 years, inclusive, with no clinically significant medical history, who are deemed by the investigator suitable to take part in this clinical study.

Treatment Groups and Duration:

Test Treatment, Dose, and Mode of Administration

Part 1:

- Fentanyl citrate (up to approximately 650 mcg), IV, administered for up to 2 hours
    - Doses of fentanyl will be titrated to produce up to an average of 50% decrease in minute ventilation. Supplemental oxygen (up to 10 L/minute by simple mask) may be administered to prevent or treat a significant decrease in oxygen saturation. It is anticipated that the majority of subjects will be administered oxygen at a rate of 2 L/minute throughout the fentanyl administrations.

Part 2:

- Fentanyl citrate (up to approximately 1100 mcg in total), IV, administered for up to 230 minutes
    - Doses of fentanyl will be titrated to produce up to an average of 50% decrease in minute ventilation. Supplemental oxygen (up to 10 L/minute by simple mask) may be administered to prevent or treat a significant decrease in oxygen saturation. It is anticipated that the majority of subjects will be administered oxygen at a rate of 2 L/minute throughout the fentanyl administrations.
- Nalmefene Autoinjector 1.5 mg (0.94% $MgCl_2$), IM, anterolateral thigh
- Narcan 4 mg, IN; into the nose

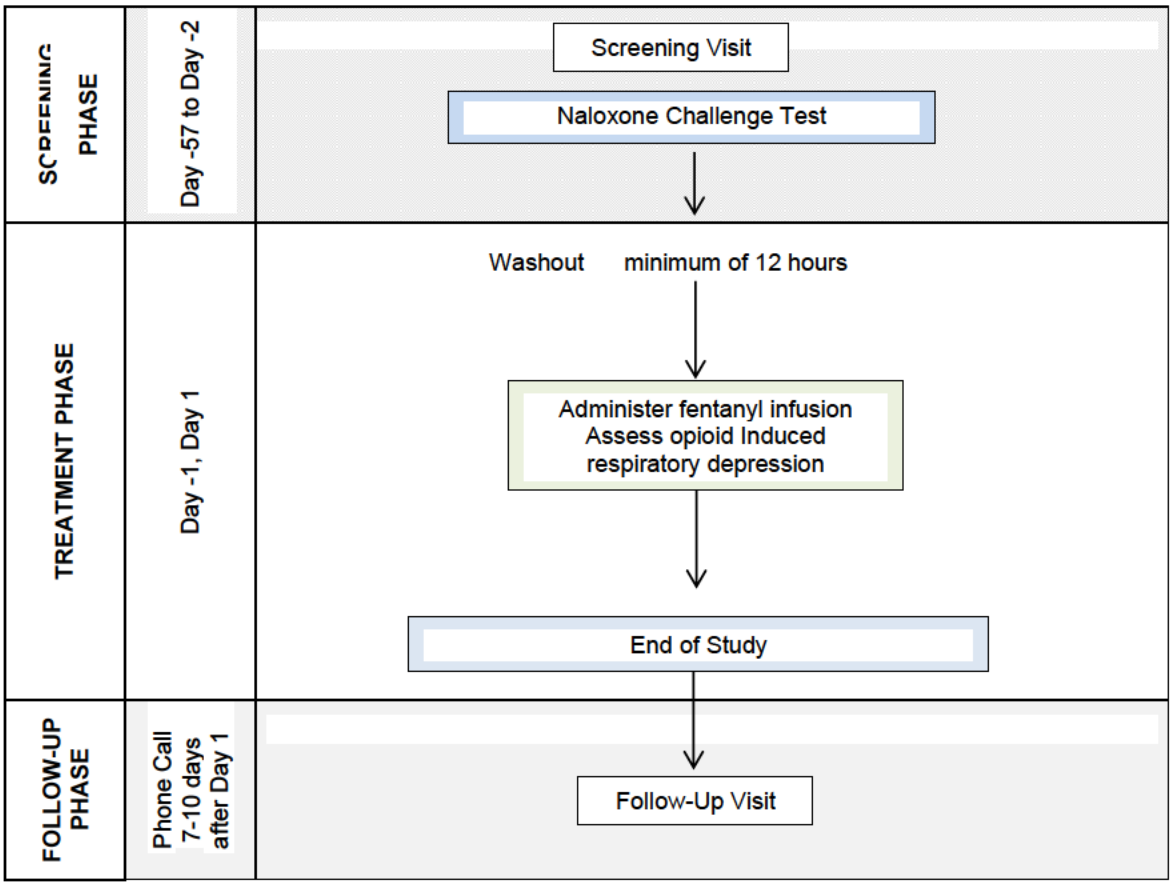
Reference Treatment, Dose, and Mode of Administration:

Parts 1 and 2:

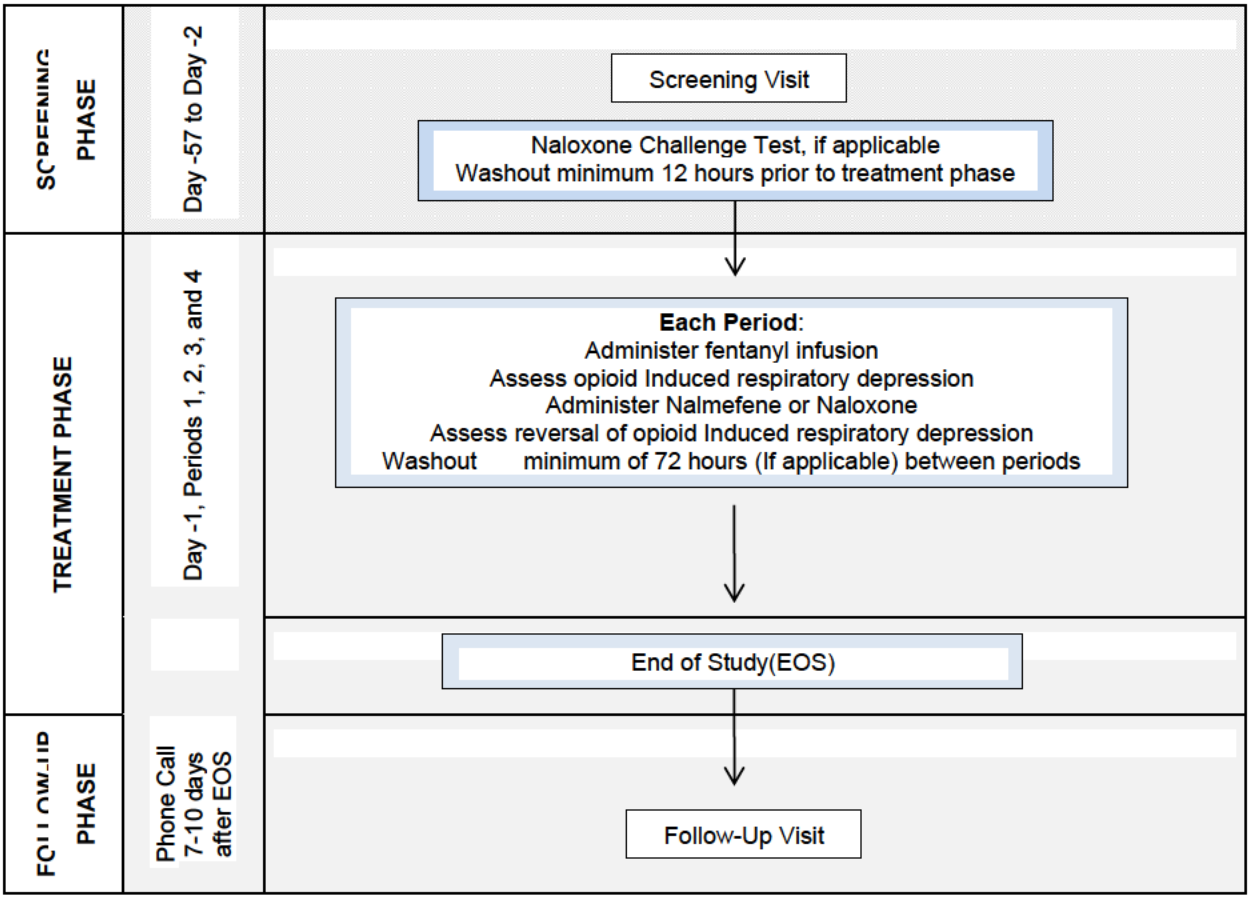
- Placebo (0.9% Sodium Chloride), IV

1.2. Schema

Part 1 Qualification Phase Study Design Graphic:



Part 2 Treatment Phase Study Design Graphic:



1.3. Schedule of Assessments

Table 1 Part 1 Study Flow Chart - Overall Procedures

Phase	Screening	Qualification			F/U	Notes
Period	**Screening**	**Check-In**	**1**	**EOS**	**F/U**	
Study Day **Study Procedures**	**-57 - -2**	**-1**	**1**	**2**	**8-11**	
Informed consent	X					
Medical history	X					Including drug and alcohol use history
Demography	X					Including weight, height, and BMI
Physical exam	X	X		X		At check-in: Symptom-directed, at discretion of investigator or designee
Inclusion/exclusion	X	X				
DSM-IV-TR (dependence)	X					
Clinical laboratory	X	X		X		Chemistry, hematology and urinalysis At check-in: chemistry and hematology testing only
Vital signs and SpO_2 with HDYF?	X	X	X	X		Taken after 5 minutes seated (or during infusions when supine, seated, or semirecumbent): heart rate, blood pressure, respiratory rate, SpO_2 Screening: Additional standing (for ~2 minutes) vital signs (heart rate and blood pressure) Obtained predose before saline infusion During fentanyl infusion: Predose, 30, and 60 minutes End of fentanyl infusion: end of infusion, 2 and 4 hrs. Time points may be added, omitted, or adjusted. Vital signs also taken pre- and post-naloxone challenge test.
Oral temperature	X	X	X	X		For safety purposes, forehead temperature may be substituted for oral. Days 1: Predose, and 8-12 hrs post infusion
Serum pregnancy test (females only)	X			X		
Serum FSH (post-menopausal females only)	X					
Urine pregnancy test (females only)		X				
Conventional 12-lead ECG	X	X		X		
Drug/alcohol screen	X	X				
Serology (HBsAg and HCV)	X					

Phase	Screening	Qualification			F/U	Notes
Period	**Screening**	**Check-In**	**1**	**EOS**	**F/U**	
Study Day **Study Procedures**	**-57 - -2**	**-1**	**1**	**2**	**8-11**	
Naloxone challenge test		X				Performed at least approximately 12 hours prior to first dose in Period 1. Includes Objective Opioid Withdrawal Scale (OOWS). Does not need to be performed if conducted during a previous check-in visit within 60 days.
RVM/capnography/ PD training and practice session	X	X				May be performed at screening or Check-in day -1 or both.
Study drug dosing			X			Time = 0, relative to other procedures. [redacted]
Respiratory volume monitoring and capnography			X			Procedure will be performed pre (Baseline) and post IV study drug administration. Predose (baseline) and continuous RVM throughout dosing and for 15 minutes after the end of the infusion for remifentanil and for 1 hr after the end of the infusion for fentanyl. Time interval may be adjusted or separate time points may be examined.
Transcutaneous CO_2 monitoring			X			Relative to fentanyl infusion, Predose (baseline) and continuous throughout dosing and for 1 hr after the end of the infusion for fentanyl. Time interval may be adjusted, or specific time points or multiple shorter intervals may be selected.
Continuous SpO_2 monitoring			X			Relative to IV dosing: Predose to 8-12 hours for fentanyl Note: For fentanyl dosings, subjects can be taken off the pulse oximetry monitoring for up to a half hour each day to shower
Follow-up phone call					X	A follow-up phone call will be made to (or received from) each subject 7 to 10 days after Day 1 or after early withdrawal from the study.
Confined to study unit		◀----------	----------	----------▶		
Concomitant therapies	◀----------	----------	----------	----------▶		
Adverse events	◀----------	----------	----------	----------▶		

EOQ: End of Qualification; F/U: Follow-up; HYDF?=How do you feel question; IV=Intravenous; RVM= respiratory volume monitor(ing);
SpO_2=Hemoglobin-O_2 saturation determined by pulse oximetry

Table 2 Part 2 Study Flow Chart - Overall Procedures

Phase	Screen-ing	Treatment						F/U	Notes
Period	**Screen-ing**	**Check-In**	**1**	**2**	**3**	**4**	**EOS**	**F/U**	
Study Day **Study Procedures**	**-57 - -2**	**-1**	**1**	**4**	**7**	**10**	**11**	**18-21**	
Informed consent	X								
Medical history	X								Including drug and alcohol use history
Demography	X								Including weight, height, and BMI
Physical exam	X	X					X		At check-in: Symptom-directed, at discretion of investigator or designee
Inclusion/exclusion	X	X							
DSM-IV-TR (dependence)	X								
Clinical laboratory	X	X					X		Chemistry, hematology and urinalysis At check-in: chemistry and hematology testing only Testing for COVID-19 may also be done at any time
Serum pregnancy test (females only)	X						X		
Serum FSH (post-menopausal females only)	X								
Urine pregnancy test (females only)		X							
Conventional 12-lead ECG	X	X					X		
Drug/alcohol screen	X	X							
Serology (HBsAg and HCV)	X								

Phase	Screening	Treatment						F/U	Notes
Period	**Screening**	**Check-In**	**1**	**2**	**3**	**4**	**EOS**	**F/U**	
Study Day **Study Procedures**	**-57 - -2**	**-1**	**1**	**4**	**7**	**10**	**11**	**18-21**	
Naloxone challenge test		X							Performed at least approximately 12 hours prior to first dose in Period 1. Includes Objective Opioid Withdrawal Scale (OOWS). Does not need to be performed: • If conducted during Part 1 and subject enters Part 2 within 60 days • If conducted on Day-1 of Part 2 within 60 days (eg. Backup subject not previously dosed).
Vital signs and SpO_2 with HDYF?	X	X	X	X	X	X	X		Taken after 5 minutes seated (or during infusions when supine, seated, or semirecumbent): heart rate, blood pressure, respiratory rate, SpO_2 Screening: Additional standing (for ~2 minutes) vital signs (heart rate and blood pressure) Days 1, 4, 7, 10: During fentanyl infusion: Predose (-15 minutes), end of infusion, 2 and 4 hrs post end of infusion. VS will also be performed on nondosing Days 2, 3, 5, 6, 8, and 9. Time points may be added, omitted, or adjusted. Vital signs also taken pre- and post-naloxone challenge test.
Oral temperature	X	X	X	X	X	X	X		For safety purposes, forehead temperature may be substituted for oral. Days 1, 4, 7, 10: Predose, and 8-12 hrs post infusion. Time points may be added, omitted, or adjusted.
Respiratory monitoring/PD training and practice session	X	X							May be performed at screening or Check-in Day -1 or both.
Randomization			X						Prior to study drug dosing in Period 1 only
Fentanyl Infusion administration			X	X	X	X			Time is relative to start of IV infusion. 3-step fentanyl infusion: first infusion at an initial rate of 5.0 mcg/min, a second infusion for 20 min and a third infusion up to 90 min. [redacted]

Phase	Screen-ing	Treatment					F/U	Notes
Period	**Screen-ing**	**Check-In**	**1**	**2**	**3**	**4**	**EOS**	**F/U**	
Study Day **Study Procedures**	**-57 - -2**	**-1**	**1**	**4**	**7**	**10**	**11**	**18-21**	
Nalmefene or Naloxone Study drug dosing			X	X	X	X			Nalmefene or Naloxone will be administered approximately 10 min following the start of Fentanyl Infusion #2. Time = 0, relative to other procedures.
Local Tolerability			X	X	X	X	X		Nalmefene Treatment only, Days 1, 4, 7, 10: Prior to the start of IV infusion Relative to Nalmefene administration: 15, 30 minutes, 1 hr and 24 hr after nalmefene administration.
Blood sample for drug concentration			X	X	X	X			Relative to Nalmefene/Naloxone administration: 2.5, 5, 10, 15, 20, and 30 minutes and at 1, 2, 4, 8, 12, and 24 hours after nalmefene/naloxone administration.
Respiratory volume monitoring and capnography			X	X	X	X			Relative to fentanyl infusion, Predose (baseline) and continuous RVM throughout dosing and for 1 hr after the end of the infusion for fentanyl. Time interval may be adjusted, or specific time points or multiple shorter intervals may be selected.
Transcutaneous CO_2 monitoring			X	X	X	X			Relative to fentanyl infusion, Predose (baseline) and continuous throughout dosing and for 1 hr after the end of the infusion for fentanyl. Time interval may be adjusted, or specific time points or multiple shorter intervals may be selected.
Continuous SpO_2 monitoring			◄----------			----------►			Relative to fentanyl infusion: Predose to 8-12 hrs post dose Time interval may be adjusted, or specific time points or multiple shorter intervals may be selected dependent on the agonist administered. Note: Subjects can be taken off the pulse oximetry monitoring for up to a half hour each day to shower.
Device deficiencies			◄----------			----------►			
Follow-up phone call								X	A follow-up phone call will be made to (or received from) each subject 7 to 10 days after EOS or after early withdrawal from the study.

Phase	**Screen-ing**	**Treatment**						**F/U**	**Notes**
Period	**Screen-ing**	**Check-In**	**1**	**2**	**3**	**4**	**EOS**	**F/U**	
Study Day **Study Procedures**	**-57 - -2**	**-1**	**1**	**4**	**7**	**10**	**11**	**18-21**	
Confined to study unit		◄----------	----------	----------	----------	----------	----------►		
Concomitant therapies	◄----------	----------	----------	----------	----------	----------	----------	----------►	
Adverse events	◄----------	----------	----------	----------	----------	----------	----------	----------►	

EOS: End of study; F/U: Follow-up; HYDF?=How do you feel question; IV=Intravenous; RVM=respiratory volume monitor(ing); SpO_2=Hemoglobin-O_2 saturation determined by pulse oximetry