CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204760Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA: 204760	Submission Date: 7/25/2014
Brand Name	MOVANTIK™
Generic Name	Naloxegol Oxalate
OCP Reviewer/Team Leader	Elizabeth Shang, Ph.D./Sue-Chih Lee, Ph.D.
OCP Division	DCP3
OND Division	DGIEP
Sponsor	Astra Zeneca
Relevant IND(s)	078781
Submission Type; Code	Original NDA, NME, Standard
Formulation; Strength(s)	12.5 mg and 25 mg IR tablets
Indication	Opioid Induced Constipation (OIC) for adult patients with chronic non-cancer pain

Introduction: The purpose of this addendum is: 1) to provide the review on the sponsor's new in vitro study result on evaluation of the inhibitory effect naloxegol on hepatic cytochrome P450 2C8 (CYP2C8) enzyme submitted on 7/25/2014, and 2) to finalize the post-marketing study (PMC) recommendation on evaluation of the impact of naloxegol on CYP2C8 enzyme.

Background: The following PMC was proposed to the sponsor at the Late Cycle Meeting: "Conduct an in vitro study to evaluate the inhibition potential of naloxegol on hepatic CYP2C8 enzyme, as this interaction has not been assessed in this NDA submission. Please refer to the FDA Draft Guidance for Drug Interaction Studies —Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations". The sponsor stated that such a study was underway and results would be available for review before the Action Date for this NDA. The Agency agreed to review the study results and determine the need for a PMR/PMC on this matter before the Action Date (Late Cycle Meeting Minutes in DARRTS on 7/10/2014).

Review of the Submission dated 7/25/2014:
The sponsor conducted an in vitro study (ADME-AZS-Wave3-140623) to evaluate the ability of naloxegol to inhibit CYP2C8 in human liver microsomes (HLM) as a reversible inhibitor. Amodiaquine (1 μM) was used as a model substrate. Quercetin (0.6667, 2, 6.667, 20, 66.67 and 200 μM) was used as a reference inhibitor. The IC_{50} for quercetin was 4.61 μM. Six concentrations (one replicate per concentration) of naloxegol (0.1, 0.3, 1, 3, 10, and 30 μM) were incubated at 37 °C with HLM and NADPH (1 mM) in the presence of the probe substrates for 10 minutes. The CYP2C8 enzyme activity (%) at various naloxegol concentrations relative to that for vehicle (DMSO) ranged from 91.3% to 108%. At tested concentration of up to 30 μM, there was little or no direct CYP2C8 inhibition by naloxegol.

Reviewer's Comment: The potential of time-dependent inhibition on CYP2C8 by naloxegol was not evaluated in this study, nor in the previous NDA submissions.

Recommendation for PMC:
Based upon the results submitted, OCP has revised the proposed PMC as follows:
Conduct an in vitro study to evaluate the time-dependent/mechanism-based inhibition potential of

naloxegol on CYP2C8 enzyme, as this interaction has not been assessed in this NDA submission. Please refer to the FDA Draft Guidance for Drug Interaction Studies —Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELIZABETH Y SHANG
09/05/2014

SUE CHIH H LEE
09/05/2014

HAE YOUNG AHN
09/05/2014

BIOPHARMACEUTICS REVIEW ADDENDUM Office of New Drug Quality Assessment			
Application No.:	NDA 204-760	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Date:	9/16/2013; 12/16/13; 4/14/14		
Division:	DGIEP	**Secondary Signature:** Tapash Ghosh, Ph.D.	
Applicant:	AstraZeneca	**Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	Movantik	**Date Assigned:**	10/25/13
Generic Name:	naloxegol oxalate	**Date of Review:**	7/8/14
Indication:	Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain	**Type of Submission:** 505(b)(1) Original	
Formulation/strengths:	IR Tablets/ 12.5 mg and 25 mg		
Route of Administration:	Oral		

In the Biopharmaceutics review dated May 16, 2014, Dr. Kareen Riviere stated that Movantik (naloxegol oxalate) 12.5 mg and 25 mg immediate release tablets are recommended for approval pending the OSI inspection results for the pivotal BE Study D3820C00018. In the OSI inspection report for Study D3820C00018 dated June 27, 2014, Dr. Chase H. Bourke stated:

> *The data generated by Quintiles Drug Research Unit (clinical site) and* (b) (4) *(analytical site) were found to be reliable. Therefore, these reviewers recommend that data generated at these sites should be accepted for Agency review.*

Thus, NDA 204-760 for Movantik (naloxegol oxalate) 12.5 mg and 25 mg immediate release tablets is recommended for approval from the Biopharmaceutics perspective.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Dr. Richard Lostritto

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KAREEN RIVIERE
07/08/2014

TAPASH K GHOSH
07/08/2014

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204-760	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Date:	9/16/2013; 12/16/13; 4/14/14		
Division:	DGIEP	**Secondary Signature:** Tapash Ghosh, Ph.D.	
Applicant:	AstraZeneca	**Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	Movantik	**Date Assigned:**	10/25/13
Generic Name:	naloxegol oxalate	**Date of Review:**	5/16/14
Indication:	Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain	**Type of Submission:** 505(b)(1) Original	
Formulation/strengths:	IR Tablets/ 12.5 mg and 25 mg		
Route of Administration:	Oral		

SUMMARY:

This submission is a 505(b)(1) New Drug Application for 12.5 mg and 25 mg of Movantik (naloxegol oxalate) immediate release tablets. The proposed indication is for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

The Biopharmaceutics review focuses on the evaluation and acceptability of:

1) the BE data bridging the Phase 3 formulation and the commercial formulation,
2) the proposed dissolution methodology,
3) the proposed dissolution acceptance criterion,
4) the dissolution data bridging the tablets containing drug substance (b) (4)
5) the dissolution data supporting a biowaiver for the 12.5 mg strength tablet, and
6) the dissolution data supporting formulation (b) (4)

A. Pivotal BE study Bridging the Phase 3 and Commercial Formulation

The Applicant conducted an *in vivo* BE Study D3820C00018 with the primary objective to demonstrate bioequivalence between the commercial naloxegol film-coated tablet 25 mg (as naloxegol oxalate) and the naloxegol film coated tablet 25 mg (as free base) used in the Phase 3 study. The BE study demonstrated that the 90% CI for the test/reference ratio for Cmax and AUC fell within FDA's BE criterion of 80-125%. Thus the commercial formulation is bioequivalent to the Phase 3 formulation.

B. Dissolution Method

The proposed dissolution method is:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	50 rpm	500 mL	37 °C	0.1 M HCl buffer

The dissolution method is acceptable.

C. Dissolution Acceptance Criterion

The proposed acceptance criterion is:

Acceptance Criteria
Q = (b) (4) % at 30 minutes

The acceptance criterion is acceptable.

D. Biowaiver for 12.5 mg Strength

The Applicant provided multi-point dissolution profile data comparing the 12.5 mg and 25 mg strengths in pH 1.2, pH 4.5, and pH 6.8 dissolution media. These data demonstrate that the dissolution profiles of the two strengths are similar in all three media. Thus, a biowaiver is granted for the 12.5 mg strength.

E. Dissolution Data Bridging the Tablets Containing Drug Substance Manufactured with (b) (4)

The Applicant provided multi-point dissolution profile data comparing tablets containing drug substance manufactured from (b) (4) and tablets containing drug substance manufactured from (b) (4) dissolution media. These data demonstrate that the dissolution profiles of the tablets containing drug substance manufactured with (b) (4)

F. Formulation Design Space

(b) (4)

RECOMMENDATION:

1. Movantik (naloxegol oxalate) 12.5 mg and 25 mg immediate release tablets are recommended for approval from a Biopharmaceutics standpoint, pending the OSI inspection results for the pivotal BE Study D3820C00018.
2. The following dissolution method and acceptance criteria for both strengths.
    i. Dissolution Method: Apparatus 2, 50 rpm agitation rate, 500 mL media volume, 37 °C, 0.1 M HCl buffer.
    ii. Dissolution acceptance criterion: (b) (4) % at 30 minutes

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Dr. Richard Lostritto

ASSESMENT OF BIOPHARMACEUTICS INFORMATION

1. Background

Drug Substance

The Applicant reports that naloxegol oxalate is highly soluble in aqueous media with solubility exceeding 50 mg/mL over the pH range of 1 to 7.5 and is classified as a BCS Class 3 (high solubility, low permeability) compound. The chemical structure is shown in Figure 1.

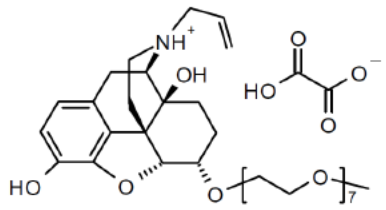


Figure 1. Chemical structure of naloxegol oxalate

Drug Product

Table 1 shows the qualitative and quantitative composition of the 12.5 mg and 25 mg proposed commercial tablet. The two tablet strengths (b) (4) are differentiated by size, weight and intagliation.

Table 1. Qualitative and Quantitative Composition of the 12.5 mg and 25 mg Proposed Commercial Tablet

		Strength (label claim)			
		12.5 mg Batch size up to (b) (4) (b) (4) tablets		25 mg Batch size up to (b) (4) (b) (4) tablets	
Ingredient (Ph Eur nomenclature / USP or NF nomenclature)	**Function**	**Quantity (mg per unit)**	**%[a]**	**Quantity (mg per unit)**	**%[a]**
Tablet core:					
Naloxegol oxalate	Drug substance	(b) (4)	(b) (4)		(b) (4)
Mannitol	(b) (4)		(b) (4)		
Cellulose, microcrystalline / Microcrystalline cellulose					
Croscarmellose sodium					
Propyl gallate					
Magnesium stearate					
Total (core tablet)		(b) (4)	100	356	100
Tablet coating[f,g]:					
Hypromellose	(b) (4)		(b) (4)		(b) (4)
Titanium dioxide					
Macrogols / Polyethylene glycol					
Iron oxide red / Ferric oxide red					
Iron oxide black / Ferric oxide black					
(b) (4)					
(b) (4)					
Total (coating)		(b) (4)	100	(b) (4)	100

Reviewer's Assessment:
The 12.5 mg and 25 mg strengths are proportionally similar in composition.

2. Pivotal BE Study to Bridge the Phase 3 and Commercial Formulations

BE Study Design

The Applicant conducted an *in vivo* BE Study D3820C00018 with the primary objective to demonstrate bioequivalence between the commercial naloxegol film-coated tablet 25 mg (as naloxegol oxalate) and the naloxegol film coated tablet 25 mg (as free base) used in the Phase 3 study (refer to Table 2).

Table 2. BE Study Description

Study title	A Phase I, Randomized, Open-label, 3 way Cross-over Study in Healthy Volunteers to Demonstrate the Bioequivalence of the Naloxegol 25 mg Commercial and Phase III Formulations and to Assess the Effect of Food Administration on the Pharmacokinetics of the Commercial Formulation
Report location	Module 5.3.1.2
Study periods:	
Clinical	First subject in: 3 July 2012. Last subject last visit: 11 September 2012.
Bioanalytical	21 August 2012 to 20 September 2012
Design	
Dose	25 mg
Single/multiple dose	Single
Number of periods	3
Two-stage design	no
Fasting/Fed	both
Number of participants:	42
Dosed	42
Completed the study	41
Included in the final statistical analysis of AUC	41
Included in the final statistical analysis of C_{max}	41

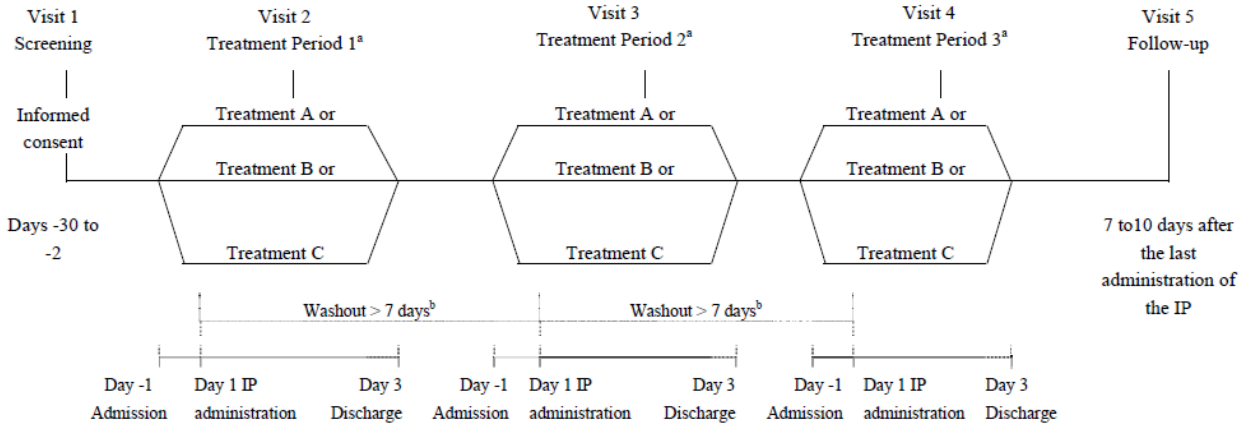
AUC: Area under the plasma concentration-time curve; C_{max}: Maximum plasma drug concentration.

Eligible healthy volunteers received investigational products (IPs) on Day 1 of each treatment period with one of the following 3 treatments administered in a crossover design in one of the 6 treatment sequences (ABC, BCA, CAB, CBA, ACB, and BAC), according to a randomized treatment sequence:

- **Treatment A**: Single oral administration of naloxogel film-coated IR tablet 25 mg commercial formulation under fasted conditions
- **Treatment B**: Single oral administration of naloxogel film-coated IR tablet 25 mg commercial formulation under fed conditions
- **Treatment C**: Single oral administration of naloxegol film-coated IR tablet 25 mg Phase III formulation under fasted conditions

Figure 2 illustrates the study design.

Figure 2. Flow Chart of Study Design



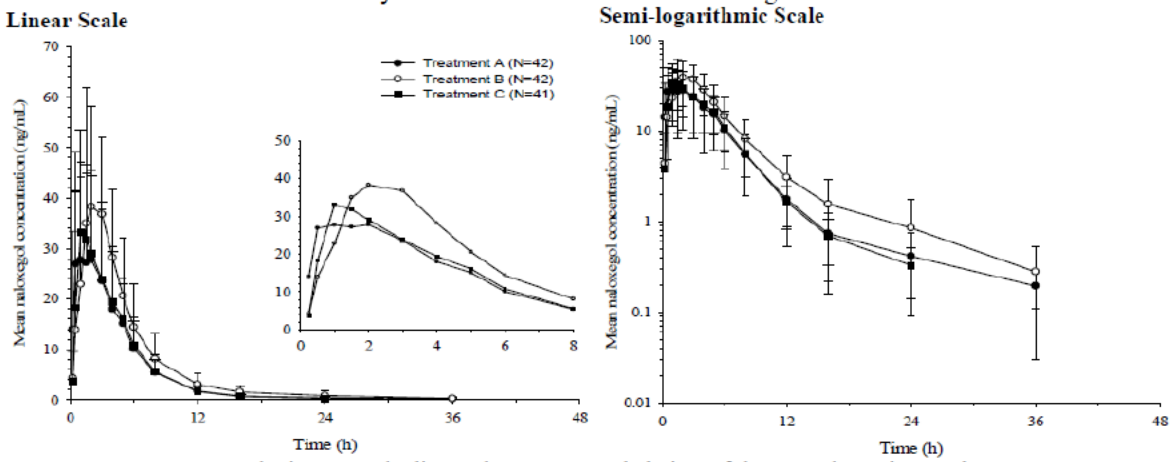
For treatments A and C, which were taken under fasted conditions, volunteers fasted for at least 10 hours prior to the first administration on Day 1. A meal was given 4 hours after dosing. A meal was also given 4 hours after dosing. For all treatments, a moderate amount of water was allowed up to 1 hour prior to dosing and 1 hour after dosing.

The Applicant calculated that a sample size of 34 evaluable subjects would provide at least 90% power to demonstrate that naloxegol commercial formulation is bioequivalent to the naloxegol Phase 3 formulation. Assuming a dropout rate less than 19%, they determined that 42 subjects needed to be enrolled.

BE Study Results

The concentration versus time profile data for naloxegol for each treatmement are shown in Figure 3.

Figure 3. Arithmetic Mean Plasma Concentration of Naloxegol (ng/mL) versus Time by Treatment on Linear and Semi-Logarithmic Scales



Note: The insets on the linear show an expanded view of the 0 to 8 hour time scale.

Table 3. Pharmacokinetic Data for Naloxegol

		Geometric least squares means (90% confidence interval), (except median [range] for t_{max})	
Parameter	**Unit**	**Test product (Commercial 25 mg naloxegol oxalate film-coated tablet)**	**Reference product (Phase III 25 mg naloxegol film-coated tablet)**
$AUC_{(0-t)}$	ng×hour/mL	142 (124-163)	152 (132-173)
$AUC_{(0-24)}$	ng×hour/mL	141 (123-160)	150 (131-171)
$AUC_{(0-\infty)}$	ng×hour/mL	145 (127-165)	153 (134-175)
C_{max}	ng/mL	38.4 (33.1-44.4)	41.5 (35.8-48.1)
t_{max}	hour	1.00 (0.23, 5.02)	1.00 (0.47, 5.00)

Table 4. Bioequivalence Data for Naloxegol

Pharmacokinetic parameter	**Naloxegol oxalate film-coated tablet/ Naloxegol film-coated tablet Geometric least squares means ratio**	**90% Confidence interval**
$AUC_{(0-t)}$	0.94	0.89 – 1.00
$AUC_{(0-24)}$	0.94	0.88 – 0.99
$AUC_{(0-\infty)}$	0.94	0.89 – 1.00
C_{max}	0.92	0.82 – 1.04

Bioanalytical Methods

The concentration of NKTR-118 in human plasma samples was determined by solid phase extraction and liquid chromatography followed by tandem mass spectrometric detection (LC-MS/MS) according to Method NKTHPP. The analytical method has a calibration range of 0.100 to 50.0 ng/mL, utilizing a 0.100 mL sample aliquot, with a validated dilution of 100-fold with human plasma.

The precision (%CV) and accuracy (% bias) for the QC samples at three concentrations were ≤6.3% and were within -5.6% to -4.5%, respectively. All study samples were analyzed within the (386 days) established stability for NKTR-118 in human plasma. QC samples represented the range of the samples analyzed. A summary is outlined in Table 5 below.

Table 5. Summary of Bioanalytical Methods Information

Test compound	Naloxegol (also known as NKTR-118 and NKTR_118), commercial formulation and Phase III formulation
Analytical matrix	Plasma (K_2-EDTA)
Analyte	NKTR-118
Internal standard (IS)	AZ13337019
Validated method	NKTHPP
Lower limit of quantification (LLOQ)	0.100 ng/mL
Validated range	0.100 to 50.0 ng/mL
Quality control (QC) levels	0.300, 5.00, 40.0, 250 ng/mL (dilution QC)
Analytical technique/method of detection	Solid phase extraction / LC-MS/MS
Total number of samples analyzed	2000
Sample storage conditions	-10 to -30°C

Reviewer's Assessment:

The BE study design is adequate. The data in Table 4 show that the point estimates of geometric mean ratios for AUCinf and Cmax were greater than 90% and that 90% CI for test/ratio for Cmax and AUC fell within FDA's bioequivalence criterion of 80-125%. This reviewer analayzed the bioequivalence data using Pheonix software version 6.2.1.51. The analysis is summarized in Reviewer's Table 1.

Reviewer's Table 1. Re-Analysis of Natural Log Transformed Data for Naloxegol

Parameter	Geomotric Mean of Test	Geomotric Mean of Reference	Ratio of Means	90% CI
AUC	142.35 ng*hr/mL	151.48 ng*hr/mL	0.940	0.888 - 0.996
AUCinf	144.65 ng*hr/mL	153.26 ng*hr/mL	0.944	0.891 - 0.999
Cmax	38.35 ng*hr/mL	41.51 ng*hr/mL	0.924	0.824 - 1.035

This reviewer's results confirm the Applicant's results. Thus, the commercial naloxegol film-coated tablet 25 mg (as naloxegol oxalate) and the naloxegol film coated tablet 25 mg (as free base) are considered bioequivanelent according to FDA standards.

OSI inspected the clinical and analytical sites for pivotal BE Study D3820C00018, and the results are pending. An addendum will be submitted to DARRTS when the OSI inspection results are available.

3. Dissolution Method

The proposed dissolution method is shown below.

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	50 rpm	500 mL	37 °C	0.1 M HCl

Overall, the proposed dissolution method is acceptable because it has adequate discriminating ability.

4. Dissolution Acceptance Criterion

The proposed acceptance criterion is:

Acceptance Criteria
Q = (b)(4)% at 30 minutes

The Applicant contends that the dissolution profile data in Figure 8 above together with the data from the relative bioavailability study D3820C00025 support that the proposed acceptance criterion is biorelevant. They conducted this BE study to investigate whether tablet variants that had been deliberately designed and manufactured to have different *in vitro* dissolution properties than the Phase 3 product. The study compared naloxegol (as free base) Phase 3 tablets (b)(4) dissolved at 30 minutes), naloxegol tablets (as naloxegol oxalate) variant fast ((b)(4) dissolved at 30 minutes) and naloxegol tablets (as naloxegol oxalate) variant slow (b)(4)% dissolved at 30 minutes) administered in the fasting state. Refer to Figure 8 for the dissolution profile data and Table 7 for the BE data.

Table 7. Summary of Results of Relative Bioavailability and Bioequivalence Study D3820C00025

		Comparison: Ratio of geometric LS means (90% CI)			
Study	**Formulations**	**Pair**	**$AUC_{(0-t)}$**	**AUC**	**C_{max}**
D3820-C00025	Form 1: 25 mg naloxegol (as oxalate) (b) (4) variant fast	Form 1/ Form 3	NAV	1.06 (0.97-1.16)	1.00 (0.88-1.13)
	Form 2: 25 mg naloxegol (as oxalate) (b) (4) variant slow	Form 2/ Form 3	NAV	1.03 (0.94-1.13)	0.97 (0.8 .10)
	Form 3: 25 mg naloxegol (as free base) film-coated tablet (Phase 3)	Form 1/ Form 2	NAV	1.03 (0.94-1.13)	1.03 (0.91-1.16)

The Applicant posits that any tablet with a dissolution profile meeting the specification of Q= (b) (4) % at 30 minutes is expected to give equivalent *in vivo* exposure to the Phase 3 tablet (and, by extension, to the commercial formulation since the Phase 3 tablet and to-be-marketed tablet are bioequivalent).

Dissolution profiles at initial, at long-term (12 months) and accelerated conditions (6 months) in HDPE bottle (30 counts) are shown in Figures 10 and 11.

Figure 10. Dissolution Profiles of Batch 12-001309AZ, 12.5 mg in HDPE bottle (30 counts)

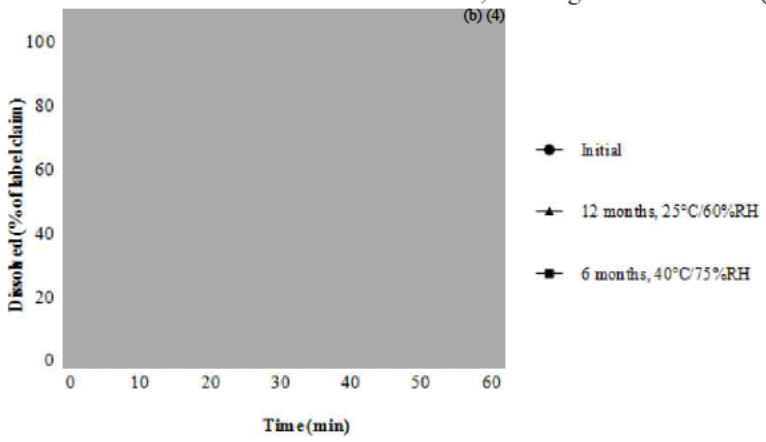
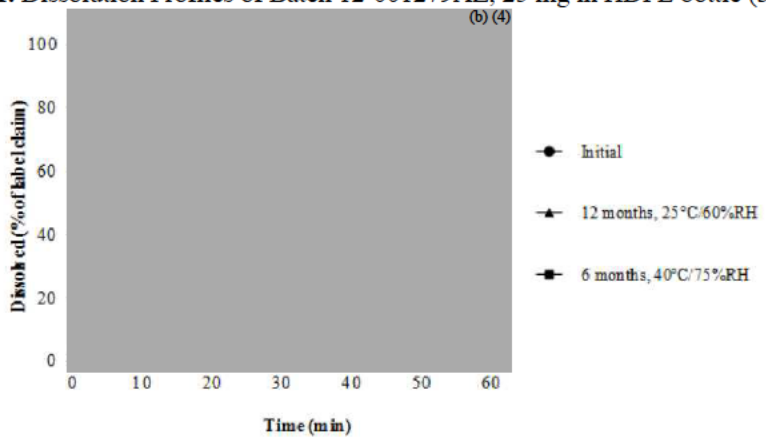


Figure 11. Dissolution Profiles of Batch 12-001279AZ, 25 mg in HDPE bottle (30 counts)



Reviewer's Assessment:

The data in Figure 8 and Table 7 support an acceptance criterion of Q= (b) (4) % at 30 minutes. This is because the fast variant (in which (b) (4) % was dissolved by 15 minutes) and the slow variant (in which (b) (4) %dissolved by 30 minutes) are bioequivalent. The dissolution profile of the commercial tablet was in between the profiles of the fast and slow variants. Therefore, the commercial formulation is considered bioequivalent to the fast and slow

variants. Additionally, proposed product with dissolution profiles that fall within the range of the profiles of the slow and fast are expected to be bioequivalent.

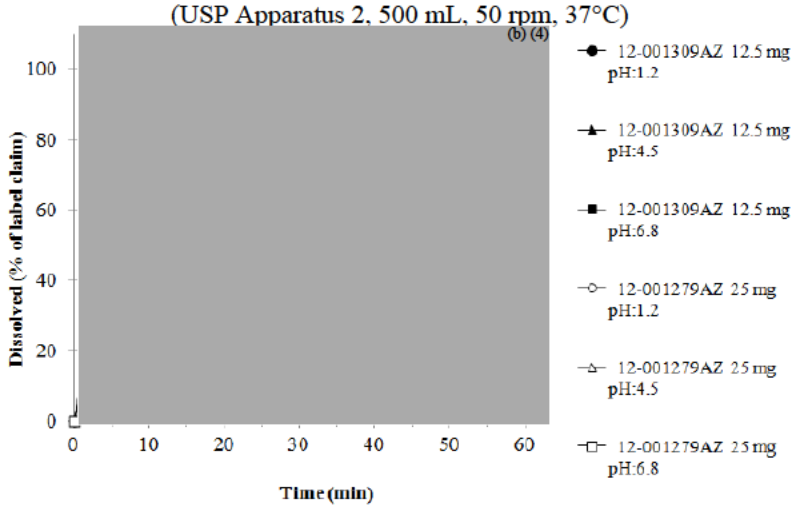
Although the proposed dissolution acceptance criterion of Q = (b) (4)% at 30 (b) (4) the Applicant does not plan to manufacture product with the formulation parameters (b) (4) Furthermore, the data in Figures 10-11 support that acceptability of the proposed dissolution acceptance criterion Thus, the proposed dissolution acceptance is acceptable.

Note that the proposed dissolution method and acceptance criterion should be used for quality control testing of the film-coated tablet. It is not acceptable to perform dissolution testing (b) (4) (b) (4) as proposed byy the Applicant in their April 14, 2014 submission.

5. Biowaiver for 12.5 mg Strength

The Applicant is requesting a waiver for demonstrating *in vivo* bioequivalence for the 12.5 mg strength of the proposed product. To support the biowaiver, they provided multi-point dissolution profile data comparing the 12.5 mg and 25 mg strengths in pH 1.2, pH 4.5, and pH 6.8 dissolution media (refer to Figure 11).

Figure 11. Mean *in vitro* dissolution profiles (N=12) of naloxegol film-coated tablets as oxalate (USP Apparatus 2, 500 mL, 50 rpm, 37°C)



Reviewer's Assessment:

A waiver for the in vivo BE studies of the lower strengths of the new tablet formulation is acceptable provided the following CFR requirements are met:

- ***Inclusion of the biowaiver request as part of the NDA submission;***
- ***The lower strength (s) and higher strength product have the same dosage form;***
- ***There is BA/BE data for the highest strength;***
- ***The lower strength (s) product is proportionally similar in its active and inactive ingredients to the highest strength product; and***
- ***Dissolution profile comparisons between the highest and lower strengths in three different media to meet the f2 similarity requirements.***

Table 1 shows that the 12.5 mg and the 25 mg are proportionally similar in composition. Also, Figure 11 shows that greater than (b) (4) of the 12.5 mg strength and the 25 mg strength dossolved by (b) (4) minutes in all media tested. As a result, the f2 similarity test is not needed to determine similarity. Overall, these data demonstrate that the dissolution profiles of the two strengths are similar in three dissolution media, as required. Thus, a biowaiver is granted for the 12.5 mg strength.

6. Bridging Study between Tablets Containing Drug Substance with Different (b) (4)

(b) (4)

7. Formulation (b) (4)

(b) (4)

(b) (4)

In Figure 14, dissolution profiles of the fastest dissolving formulation, slowest dissolving formulation, and the 2 center point batches are compared.

(b) (4)

Reviewer's Assessment:

In this DOE study, many parameter deviation were conducted simulatneously. (b) (4)

The following comment was conveyed to the Applicant in an IR letter dated March 12, 2014.

FDA Comment
Your proposal to have a [redacted] (b) (4)

Applicant's Response
AstraZeneca [redacted] (b) (4)

In a submission dated April 14, 2014, the Applicant agreed [redacted] (b) (4) (b) (4) (b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KAREEN RIVIERE
05/16/2014

TAPASH K GHOSH
05/16/2014

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 204760	Submission Date(s): 09/16/2013, 11/14/2013, 12/16/2013, 01/21/2014, 01/30/2014, 02/14/2014, 02/24/2014, 04/10/2014, 05/05/2014
Brand Name	To be determined
Generic Name	Naloxegol Oxalate
OCP review team	Sandhya Apparaju *[Primary Reviewer]* Elizabeth Shang *[In vitro study review]* Sue Chih Lee *[DCP3 Team Leader]* Justin Earp *[Pharmacometrics Reviewer]* Nitin Mehrotra *[Pharmacometrics TL]* Yuzhuo Pan *[PBPK- Primary Reviewer]* Ping Zhao *[PBPK- Secondary Reviewer]*
OCP Division	DCP3
OND Division	DGIEP
Sponsor	Astra Zeneca
Relevant IND(s)	078781
Submission Type; Code	Original NDA, NME, Standard
Formulation; Strength(s)	12.5 mg and 25 mg IR tablets
Indication	Opioid Induced Constipation (OIC) for adult patients with chronic non-cancer pain

Table of Contents

1 Executive Summary

Naloxegol is a 7-pegylated derivative of naloxone. It is designed to be a peripheral mu-opioid receptor antagonist for treatment of opioid induced constipation (OIC) in chronic non-cancer pain patients. The proposed oral dose is 25 mg once daily. The formulation proposed is an immediate release tablet of naloxegol oxalate. Sponsor has conducted phase I studies for evaluating the pharmacokinetics, pharmacodynamics, drug-drug interactions, specific population PK and safety, mass balance, QT prolongation potential, relative bioavailability and food-effect of naloxegol. In addition, population PK, exposure-response and PBPK analyses are provided. The clinical program in patients consisted of a phase 2b study conducted using 5, 25 and 50 mg *qd* doses of naloxegol, as well as two pivotal 12 week efficacy & safety trials in OIC patients evaluating two doses of naloxegol (12.5 mg and 25 mg *qd* versus placebo) and associated long-term safety extension studies. Twelve in vitro studies were conducted to evaluate absorption, distribution, metabolism characteristics and drug-drug interaction potential of naloxegol. Validated analytical methods were employed in the analyses of naloxegol, naloxegol-glucuronide, and naloxone in plasma and urine samples across studies.

1.1 Recommendation

NDA 204760 Naloxegol Oxalate for Opioid-induced-constipation in chronic, non-cancer pain patients is acceptable from a Clinical Pharmacology perspective, pending an agreement with the sponsor related to the labeling language.

1.2 Phase IV Commitment

Conduct an *in vitro* study to evaluate the inhibition potential of naloxegol on hepatic CYP2C8 enzyme, as this interaction has not been assessed in this NDA submission. Please refer to the FDA Draft Guidance for Drug Interaction Studies —Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Dose/ Exposure-response findings: Dose-response in terms of efficacy and safety was assessed in a phase 2b clinical trial in OIC patients (5 mg *qd*, 25 mg *qd*, 50 mg *qd* vs. placebo); due to the absence of significant efficacy outcomes, the 5 mg *qd* dose was not evaluated further in the phase 3 trials, while the 50 mg *qd* dose was also not carried into phase 3 due to increased abdominal adverse events and discontinuations at this dose level.

In addition, the phase 3 pivotal efficacy and safety trials evaluated two doses of naloxegol (12.5 mg *qd* and 25 mg *qd*) against placebo allowing exploration of dose-response. The primary efficacy endpoint was percentage responders during the 12 week treatment period relative to placebo.

Based on the applicant's primary efficacy analysis, there is a trend in dose-response for the efficacy of naloxegol with modest increase in response rates between 12.5 and 25 mg dose groups. Response rates for the primary endpoint in study 04 are 29.4%, *40.8%, *44.4% for placebo, 12.5 and 25 mg arms. Response rates for the replicate study 05 are 29.3%, 34.9%, *39.7% for placebo, 12.5 and 25 mg arms (* denotes statistical significance indicating that the lower dose of 12.5 mg did not meet the statistical significance in trial 05). The 25 mg dose is most effective and the efficacy conclusions are consistent across all secondary endpoints.

Exposure-response analysis for the primary efficacy endpoint showed a significant relationship between exposures and response which is consistent with the dose response, suggesting that higher exposures lead to better response. The significant exposure-response analysis provides supportive evidence of effectiveness for the naloxegol in the treatment of opioid induced constipation. Moreover, the shallow exposure-response analysis also indicates that lower exposures compared to that observed with 25 mg may not result in a meaningful loss of efficacy.

Dose- and exposure-response relationships were also evident for gastrointestinal adverse events. In particular abdominal pain was evaluated by severity and relationships for moderate & severe and severe AEs was considered to be shallow. Dose-response was also apparent for discontinuations due to withdrawal events. Discontinuations

were 2-fold higher for the 25 mg compared to 12.5 mg dose group, due to adverse events. However, the drug was fairly well tolerated overall with < 20% of patients discontinuing in the 25 mg group due to adverse events.

Dosing recommendations: The sponsor's proposed dose of 25 mg appears reasonable for those that can tolerate it (>85% of patients in phase 3 studies 04 and 05). However, because of the numerical trend in dose response and shallow exposure response relationships for efficacy, the question arises as to whether patients who cannot tolerate the 25 mg dose would benefit from the 12.5 mg dose. Because patients who did not tolerate the 25 mg dose did not receive 12.5 mg subsequently in the registration trials, the question was asked: Do patients with abdominal pain have a different response compared to those who do not? This question was driven by two pharmacological aspects: 1) abdominal pain may be a symptom of opioid withdrawal; 2) abdominal pain may also be an indicator of efficacy. Both the primary and secondary endpoints were evaluated with regards to the occurrence of abdominal pain. In general, patients with abdominal pain AEs had consistently higher response rates for both the primary and secondary endpoints. Based on this observation in combination with a shallow exposure-response relationship and apparent dose-response in both studies, we recommend for patients who cannot tolerate the drug due to abdominal pain, to reduce their dose to 12.5 mg prior to discontinuing the drug.

QT prolongation potential: While there is an apparent exposure response relationship for naloxegol effect on the QT interval the IRT division concluded there was no significant QTc prolongation effect of nalexogol in the TQT study. The largest upper bound of the 2-sided 90% CI's for the mean differences between 150 mg naloxegol (supra-therapeutic dose) and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.

Potential for formation of naloxone: Because naloxegol is PEGylated naloxone, formation of naloxone by complete separation of the 7-pegylated side chain is a theoretical possibility. Based on the information available from phase I trials and in vitro studies, naloxone concentrations ≥ 0.25 ng/mL (LLOQ for the assay) can be ruled-out. The presence of naloxone at concentrations below 0.25 ng/mL nor the clinical relevance of such low concentrations in causing central opioid antagonism is not known.

Potential for the formation of EG, DEG and metabolites: Because of the PEGylated side-chain on naloxegol and metabolism by sequential removal of ethoxy units, it was considered whether there is a likelihood for the formation of ethylene glycol (EG) and diethylene glycol (DEG) and their toxic metabolites such as glycolic acid, oxalic acid etc. The likelihood that significant amounts of such toxic metabolites are formed after naloxegol administration and accumulate to toxic levels after naloxegol administration is low. Even when assuming the worst-case scenario i.e., all PEG in naloxegol was metabolized to EG, DEG, or OA which, based on metabolic profiling is a significant overestimation, the metabolite concentrations after daily dosing would still be below the reported safe or minimally toxic daily doses in humans. The Pharmacology/Toxicology reviewers for the NDA also concur with the sponsor's estimations in this regard.

Pharmacokinetics:

Naloxegol PK is dose- and time-independent, with dose proportional increases in AUC and slightly more than dose proportional increases in Cmax. PK variability was moderate (27- 55 %). Daily dosing results in minimal accumulation.

Absorption: Absorption occurs after oral dosing with a median Tmax of 1 to 1.5 h. Double peaks are seen in most individuals. The reason for this observation is unclear. Food increases naloxegol Cmax and AUC (by 47 % and 55 %, respectively, for the Phase 3 formulation and by 30 % and 46 % respectively, for the commercial formulation) However phase 3 trials were conducted in fasted conditions and hence the labeling proposes dosing on an empty stomach as well. Absolute bioavailability was not evaluated for this drug.

Distribution: The mean apparent volume of distribution during the terminal phase (Vz/F) in healthy volunteers ranged from 968 to 2140 L. The plasma protein binding of naloxegol is low (4.2 %). There is no concentration-dependent effect on protein binding.

Metabolism: Based on in vitro studies, CYP3A4/5 appear to be the major isoforms for the metabolism of naloxegol, while CYP2D6 appears to have minor contribution. Based on all the information available (including mass balance

and drug interaction data), metabolism appears to be the predominant route of clearance. Metabolism of naloxegol occurs by partial removal of ethoxy units from the PEG side-chain as well as other oxidative reactions. There were no major metabolites (i.e. > 10 %) for naloxegol. Naloxegol glucuronide was below detection in plasma at clinically relevant doses.

Excretion: The terminal elimination half-life across phase I studies was variable, ranging from 6-11 hours. Half-life of naloxegol in patients was somewhat longer at steady-state (14 h) vs. those noted in healthy volunteer PK studies. In a mass balance study in healthy volunteers, naloxegol had an average recovery of 84 %. 16 % of radioactivity dose was found in urine, with 10 % as unchanged drug and 6 % as metabolites. In feces, ~ 68 % of radioactivity dose was found; 58 % of fecal radioactivity was characterized, with 16 % noted to be unchanged drug and remaining as metabolites. A biliary excretion component for naloxegol may be suggested by the appearance of secondary peak in the PK profile suggestive of enterohepatic recirculation, but this was not formally assessed.

PK in patients: PK variability was comparable in healthy volunteers and OIC patients. Cmax and AUC values in OIC patients (Phase 2b) were roughly twice those noted in healthy volunteers dosed with naloxegol alone in various phase I drug-drug interaction studies. However, due to differences in sample sizes across the phase I studies (n = ~22) and the PK sub-study in phase 2b (n = 9-12), and up to 55 % variability in the PK of naloxegol, it is difficult to comment whether these differences are real.

Specific Populations:

Race: Caucasians appear to have modestly higher systemic naloxegol exposure (20 %) and lower clearance values compared to Japanese or African-Americans based on a cross-study comparison in small sample size populations.

Age: In a Japanese PK study, elderly volunteers on average had ~ 30 % and 45 % higher naloxegol Cmax and AUC_{tau} at steady-state compared to younger subjects. In clinical trials of naloxegol, elderly (> 65 years) represented ~ 11 % of the trial population. No dosage adjustment is proposed for the elderly, however safety in elderly in general needs to be monitored due to potential for increased exposure, as well as reduced renal function (which in turn may have effects on metabolism and transport processes; note some individuals with unusually high exposures in the renal PK study) and increased sensitivity to some medications in the elderly.

Hepatic Impairment: Although naloxegol appears to be extensively metabolized, there was no impact of mild to moderate hepatic impairment on the pharmacokinetics of naloxegol. There are no PK, efficacy or safety data in subjects with severe hepatic impairment.

Renal Impairment: Renal clearance appears to be a minor pathway for naloxegol based on overall information. In a PK study in moderate (n= 8), severe (n = 4), and ESRD (n =4) patients not yet on dialysis, there was an average increase of 70 %, 131 %, and 98 % for AUC and 18 %, 86 %, and 107 % increase in Cmax in these renal impairment subgroups compared to the control group . Four individuals belonging to the moderate to ESRD groups appeared to drive up the averages with individual increases of up to 5-fold increase over normal group in Cmax and up to 8.4-fold for AUC; these differences in exposure couldn't be attributed to any particular factor based on available demographic, disease and concomitant medication history of these subjects and as such subjects couldn't be ruled out as outliers in this small sample size study. As such, it is advisable to start patients on renal impairment (moderate, severe or ESRD) on a lower dose of naloxegol (e.g. 12.5 mg *qd*). Dose may be increased by the physician is adequate efficacy was not noted and safety was acceptable at the lower dose. ESRD subjects (n = 8) on dialysis had systemic exposures comparable to that of the control subjects, and very little drug was removed by dialysis.

Drug-drug interactions:

In vitro findings:

Naloxegol as a substrate: Naloxegol is a substrate for CYP3A drug metabolizing enzyme and P-gp efflux transporter; therefore drugs that are inhibitors or inducers of these systems are likely to modulate naloxegol pharmacokinetics. It does not appear to be a substrate for other major CYP450 enzymes and transporters.

Naloxegol as an inhibitor or inducer: Naloxegol did not cause inhibition or induction of major CYP enzymes and transporters *in vitro* at clinically relevant concentrations.

In vivo findings:

Based on the *in vitro* findings, the in vivo drug-drug interaction studies focused on the effects of inhibitors or inducers of CYP3A4 enzyme and/or P-gp transporter on the PK of naloxegol:

Strong CYP3A4/P-gp Inhibitors: Co-administration with ketoconazole, a strong CYP3A4/P-gp inhibitor, resulted in 11-fold and ~ 12.85-fold increases in Cmax and AUC of naloxegol. Therefore dosing with such drugs is contraindicated.

Use with grapefruit juice, which can be a strong CYP3A inhibitor, was not formally evaluated but we recommend avoiding concomitant use of naloxegol with such foods due to a potential for increased exposure.

Moderate CYP3A4/P-gp Inhibitors: Co-administration with moderate CYP3A4 inhibitor diltiazem resulted in 2.86-fold and 3.4-fold increase in Cmax and AUC; dose reduction to 12.5 mg *qd* is proposed by the sponsor for use with moderate CYP3A4 inhibitors. Considering the potential for increased adverse events particularly of the abdominal origin, we recommend that concurrent dosing with moderate CYP3A4 inhibitors should be avoided. If dosing with moderate CYP3A4 inhibitor drugs cannot be avoided, then reduce dose to 12.5 mg *qd* and use with caution.

P-gp Inhibitors: Co-administration with quinidine, a P-gp inhibitor, resulted in a 2.4-fold and 1.4-fold increase in Cmax and AUC of naloxegol; dosing proposal for P-gp inhibitors follows their corresponding CYP3A4 inhibitor potential; for e.g. P-gp inhibitors which are also strong or moderate CYP3A4 inhibitors should follow the dosing proposals for those inhibitor class of drugs (i.e. contraindication or dose-reduction, respectively), while P-gp inhibitors that are weak CYP3A4 inhibitors do not need dose adjustment.

CYP3A4/P-gp Inducers: CYP3A4 inducer rifampin reduced naloxegol exposure by 89 % (AUC); therefore use with rifampin is not recommended due to potential for loss of efficacy. Use of 25 mg *qd* with moderate CYP3A4 inducers is supported by PBPK simulations using efavirenz, which suggested a 50 % reduction in naloxegol exposure.

Morphine: Naloxegol did not appear to alter morphine pharmacokinetics.

Physiologically-based- Pharmacokinetics (PBPK) Modeling in support of DDI: The sponsor's PBPK model reasonably predicted the observed effect of various CYP3A modulators. The simulations confirmed the predominant contribution of CYP3A metabolism for naloxegol, and predicted the effect of other moderate or weak CYP3A inhibitors on naloxegol exposure. Please refer to the PBPK review in the appendices for details.

2 Question Based Review

2.1 General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Naloxegol (MW: 741.8) is a pegylated derivative of naloxone and is manufactured as the oxalate salt. Naloxegol oxalate is a (b) (4) salt (b) (4) that has been seen during process development and manufacture. The structure of naloxegol oxalate is as follows:

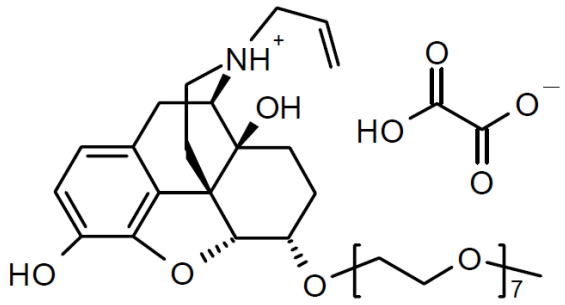


Figure 1: Structure of Naloxegol Oxalate (Source: Sponsor's submission)

Systematic chemical name (IUPAC): (5α, 6α)-17-allyl-6-(2,5,8,11,14,17,20-heptaoxadocosan-22-yloxy)-4,5-epoxymorphinan-3,14-diol oxalate. The melting point of naloxegol oxalate is 92°C. Naloxegol oxalate exhibits two pKa values; 8.4 (amine) and 9.5 (phenol). The partition coefficient, log P (octanol/water), was determined to be 1.4 (25°C). Solubility of naloxegol in water is > 50 mg/mL. The drug product is an oral, immediate release solid dosage form. The presentation of the formulation is that of oval, biconvex, mauve, film-coated tablet.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Physiological effects of opioids in the gastrointestinal tract are caused by binding at opioid receptors within the enteric nervous system and include decreased motility, decreased secretions, increased absorption of fluid from intestines and increased sphincter tone, which may cause constipation in individuals who take opioids. Naloxegol is PEGylated derivative of naloxone, and functions as a peripherally-acting mu-opioid receptor antagonist (PAMORA) in the gastrointestinal tract, thereby decreasing the constipating effects of opioids. It is indicated for the treatment of Opioid-Induced-Constipation (OIC) in chronic non-cancer pain.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The proposed dose of naloxegol oxalate for most patients is 25 mg *qd* by oral route. Dose reduction to 12.5 mg *qd* is proposed for patients who take moderate inhibitors of CYP3A4.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In support of the NDA, sponsor submitted 18 phase 1 study reports, one phase 2 dose-ranging study, 5 phase 3 efficacy and safety and long-term safety extension trials, as well as 12 in vitro study reports to evaluate the absorption, distribution, metabolism and drug-interaction potential characteristics of naloxegol and metabolites.

The phase I studies included open-label, parallel group, ascending single and multiple dose pharmacokinetic studies and, pharmacodynamics studies evaluating effects of rising doses on the central (pupillary constriction) and peripheral (orocecal transit) effects of naloxegol in healthy volunteers. Other phase 1 studies included 4 single dose, crossover drug-drug interaction studies in healthy volunteers to evaluate PK and safety with ketoconazole, diltiazem, quinidine, rifampin, and 2 single dose, parallel group, specific populations PK and safety studies in subjects with various degrees of renal or hepatic impairment.

NDA also includes a placebo- and active-controlled, thorough QT study using therapeutic and supra-therapeutic doses of naloxegol. A study in Japanese volunteers evaluated single and multiple dose (*QD*) pharmacokinetics, effect of age (young vs. elderly) and food-effect on PK. Metabolite analyses study reports evaluated metabolic profile and percentages in greater detail from the phase I studies.

Additionally, one PBPK report as well as three population PK and exposure-response reports are included. Two relative bioavailability/BE studies evaluated bioavailability of the phase 1, or Phase 3 formulations with each other or with respect to the commercial (oxalate) formulation as well as the food-effect of these formulations. A mass balance study using radio-labeled naloxegol in six healthy adult volunteers evaluated the recovery of

radioactivity in urine, plasma and feces. Additionally, several bioanalytical method validation and assay reports in plasma and urine have also been submitted.

In vitro studies characterized in established systems the permeability, protein-binding, substrate, inhibitor or inducer potential of naloxegol for various enzymes and transporters. The phase 2b study evaluated 5, 25 and 50 mg naloxegol in OIC patients using a double-blind, randomized, placebo-controlled, multiple-dose study. Two phase 3 trials evaluated efficacy and response of naloxegol 12.5 mg and 25 mg *qd* against placebo in chronic non-cancer pain patients with OIC over 12 week duration. Two other trials evaluated a 12-week and a 52 week extension study of phase III patients to evaluate long term safety and tolerability.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Based on the mechanism of action (peripheral mu opioid receptor antagonism), and the claim that the PEGylation of naloxone and its P-gp substrate characteristics do not allow blood brain barrier permeability and thus antagonism of central effects of opioids, sponsor included exploratory pharmacodynamic evaluations in two phase I trials. Peripheral antagonistic effect of PEG7-Naloxol was evaluated by mean % change in orocecal transit time. Lactulose was given to evaluate orocecal transit time by means of the hydrogen breath test. The orocecal transit time was defined as the time between lactulose ingestion and the earliest detectable rise in hydrogen >5 ppm above baseline for 3 consecutive samples. The central antagonism was assessed by evaluating effect of naloxegol on morphine induced pupillary constriction (miosis) in volunteers. The % change in mean pupil diameter over time (AUC) was calculated in different light and dark conditions.

In clinical trials, the responder rates in treatment and placebo groups were evaluated as the primary endpoints using the incidence of spontaneous bowel movements (SBMs) i.e. without the use of rescue laxative. In phase 3 trials, a responder was defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 9 out 12 weeks and at least 3 out of the last 4 weeks. Several other secondary endpoints were also assessed including change from baseline in the number of SBMs, time to first SBM after initiation of treatment, change from baseline in degree of straining, change from baseline in stool consistency etc. Please refer to the Clinical review for further information in this regard.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, naloxegol in plasma and other biological specimens were adequately assessed using validated HPLC method with MS/MS detection or LC-API with MS/MS detection methods. Please refer to the analytical section 2.6., of this review for further information.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Dose-response for naloxegol in a Phase 2 trial in chronic non-cancer OIC patients:

In the phase 2b trial of naloxegol, three doses (5 mg, 25 mg and 50 mg *qd*) were evaluated against placebo for four weeks. The original plan to evaluate a 100 mg *qd* dose was dropped due to gastrointestinal adverse event frequency at the 50 mg *qd* dose level.

Efficacy was defined as the change from baseline in the number of spontaneous bowel movements (SBMs) during the first week of double-blind study; SBM change from baseline and frequency data at other weeks were additional secondary endpoints in this trial.

There was a trend for dose-response both at week 1 (primary efficacy variable) and the average of all four weeks with respect to change from baseline in SBMs while on naloxegol. Mean number of SBMs per week increased with

dose: 4.2, 4.6 and 6.2 at 5, 25 and 50 mg *qd*. The p-value relative to placebo was significant for the 25 mg *qd* (except at week 2) and the 50 mg *qd* doses but not the 5 mg *qd* dose of naloxegol. For all weeks combined, p-value < 0.05 was noted for the 25 mg and 50 mg *qd* doses of naloxegol.

Time to first laxation was significant for naloxegol relative to placebo for the 25 mg and 50 mg *qd* dose groups; median time to first laxation was 6.2 h, 6.6 h and 2.9 h for the 5, 25 and 50 mg *qd* doses, respectively. For comparison, the median time to first laxation for the corresponding placebo groups were 28.2, 48.6 and 44.9 h, respectively for the three dose cohorts.

Table 1: Change from baseline in SBMs/week in the Phase 2 OIC population

Mean (SD)	**Placebo N = 31**	**5 mg *QD* N = 31**	**Placebo N = 27**	**25 mg *QD* N = 29**	**Placebo N = 37**	**50 mg *QD* N = 30**
Run-in	1.5 (2.0)	0.7 (1.9)	1.2 (2.2)	1.4 (1.6)	0.9 (2.2)	1.4 (2.1)
Week 1	1.8 (2.4)	2.6 (3.6)	1.9 (2.5)	3.6 (2.3)	1.9 (5.2)	4.4 (3.8)
Week 2	1.7 (1.7)	2.1 (2.7)	2.5 (3.7)	2.8 (2.1)	1.0 (1.7)	4.3 (3.6)
Week 3	1.5 (2.3)	2.3 (3.2)	1.4 (1.9)	3.1 (2.9)	1.1 (2.1)	5.2 (4.4)
Week 4	1.7 (2.4)	2.1 (3.0)	1.0 (2.2)	3.5 (2.3)	0.7 (1.9)	3.9 (3.9)
Weeks 1-4	***1.7 (1.9)***	***2.3 (2.9)***	***1.7 (2.2)***	***3.2 (2.0)***	***1.2 (2.0)***	***4.6 (3.4)***

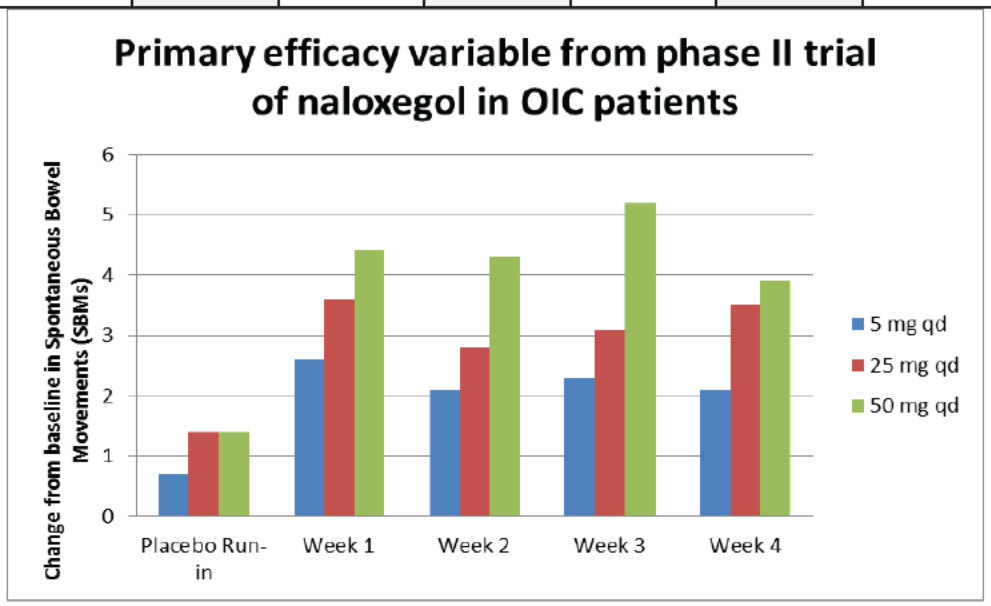


Figure 2: Dose-response trends for naloxegol doses in phase 2b trial

Sponsor's post-hoc analysis of proportion of responders (those with increase of at least 2 SBMs over baseline) suggests significant increase with the 25 mg *qd* (75 % vs. 26 % in placebo) and 50 mg *qd* (92 % vs. 29 % in placebo) dose groups, compared to a non-significant decrease at the 5 mg *qd* dose relative to placebo (38 % vs. 41 % placebo) suggesting lack of efficacy at the 5 mg *qd* dose level.

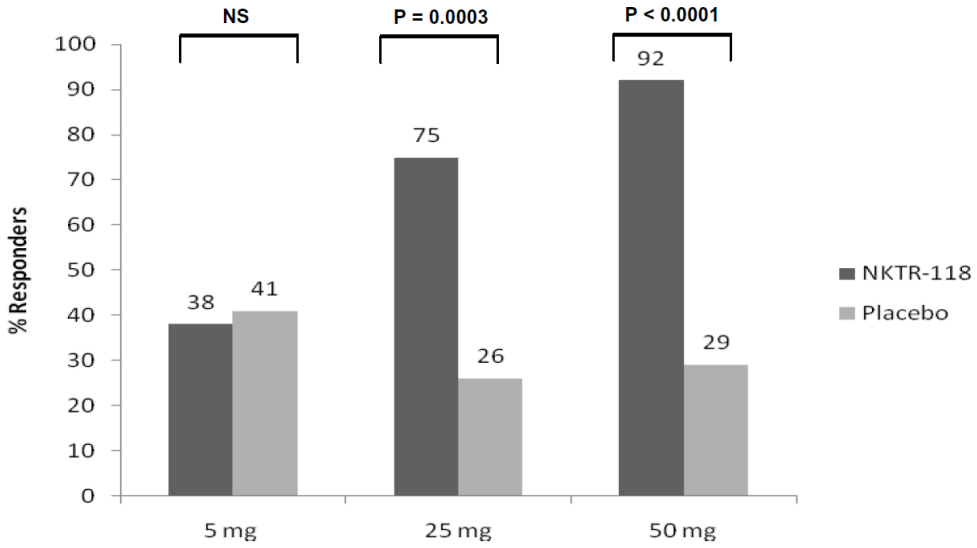


Figure 3: Responder rates (phase 2) for naloxegol (NKTR-118) by dose (Sponsor's analysis)

Dose-response information from phase 3 efficacy trials of naloxegol in OIC:

Two randomized, double-blind, parallel group, placebo-controlled, 12-week, Phase 3 efficacy and safety trials of naloxegol in OIC patients were conducted using 12.5 mg *qd* and 25 mg *qd* doses versus placebo. Per sponsor, the 25 mg dose was chosen based on the observed risk benefit profile in the Phase 2b study. The 5 mg *qd* dose and the 50 mg *qd* dose evaluated in the phase 2b trial were not carried into phase 3 due to concerns with efficacy (insignificant increase in SBMs over baseline), and safety (abdominal pain events), respectively. The 12.5 mg dose was included in phase 3 to better understand the minimal effective dose. The primary efficacy endpoint in phase 3 trials was the responder rates. A responder was defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 9 out 12 weeks and at least 3 out of the last 4 weeks. Please refer to the clinical and statistical reviews for a complete review of study findings. The following is a summary of dose-response trends based on sponsor's data:

For the clinical trial D3820C00004, for the primary efficacy variable, there was a statistically significant higher response rate in the NKTR-118 25 mg (p=0.001) and 12.5 mg (p=0.015) groups compared with placebo over 12 weeks in patients with OIC. In the clinical trial D3820C00005, for the primary efficacy variable, statistically significant differences against placebo were noted only for the higher 25 mg *qd* naloxegol dose, but not the 12.5 mg *qd* dose in this trial. Numerically, responder rates were lower for the two naloxegol dose groups in study 005 compared to study 004.

Table 2: Responder rates from naloxegol pivotal phase 3 trials

Phase 3 Clinical Trial 004			
Treatment	N	% responders	p-value vs. placebo
Placebo	214	29.40%	NA
12.5 mg *qd*	213	40.80%	0.015
25 mg *qd*	214	44.40%	0.001
Phase 3 Clinical Trial 005			
Treatment	N	% responders	p-value vs. placebo
Placebo	232	29.30%	NA
12.5 mg *qd*	232	34.90%	0.202
25 mg *qd*	232	39.70%	0.021

Based on the applicant's primary efficacy analysis (Figure 4), there is an evident shallow numerical trend in dose-response for efficacy of naloxegol. This analysis indicates that the 25 mg dose is most effective and is consistent across all the secondary endpoints (see the pharmacometrics review in the Appendix).

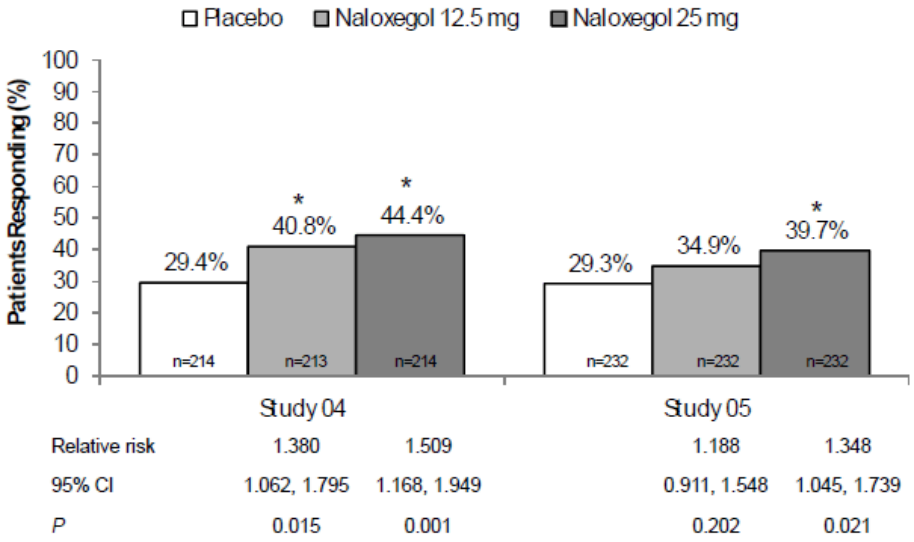


Figure 4: Sponsor's primary efficacy analysis for phase 3 trials 04 and 05 (Source: Sponsor's Clinical Summary of Efficacy, Figure 2)

Exposure-response for efficacy: Exposure-response analysis was consistent with dose response, suggesting that higher exposures led to better response.

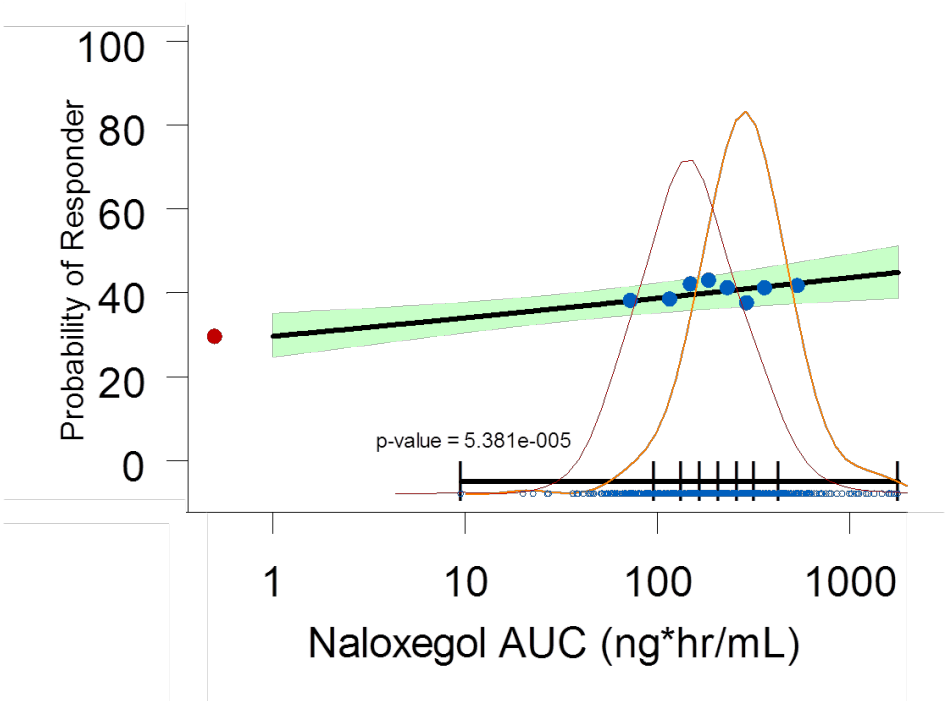


Figure 5: Logistic regression for the primary efficacy endpoint (SBM responder, intent-to-treat analysis set) suggests that those with higher exposures exhibited the best response. Scatter points represent the probability of response for each exposure bin or placebo (red). Solid line is the logistic regression and the shaded region is the prediction interval.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

Safety findings from the phase 2 dose ranging study suggest increased adverse event frequency particularly of the gastrointestinal origin in the naloxegol treatment group, particularly at the highest dose of 50 mg *qd*. GI disorders included diarrhea, abdominal pain and nausea.

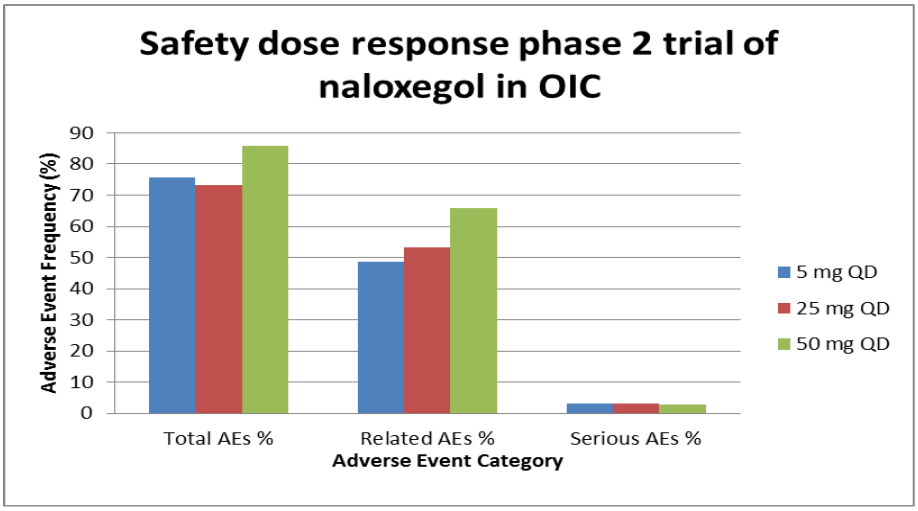


Figure 6: Dose-response trends for adverse events (Phase 2b trial)
The only drug-related serious adverse event was found in the 50 mg qd dose group and described as upper abdominal pain.

Total discontinuation rates in the phase 2b study were 13.9, 6.5, and 37.8 % for the 5 mg, 25 mg and 50 mg *qd* doses respectively. Corresponding discontinuations in the placebo group were 13.9 %, 0 % and 15.4 %, respectively at the three doses evaluated. Thus there was an increase in discontinuations with dose and over placebo, particularly at the 50 mg *qd* dose.

Safety dose-response information for phase 3 trials: In the clinical trial 004, safety findings suggest that the adverse event frequency was higher with the 25 naloxegol dose compared to placebo or 12.5 mg *qd*. These rates were 46.9 %, 49.3 % and 61.2 % in the placebo, 12.5 mg and 25 mg *qd* doses. There were 5.2 %, 5.2 % and 3.3 % patients with serious adverse events in the placebo, 12.5 mg and 25 mg groups of naloxegol. Percentage discontinuations due to adverse events were 5.6 %, 4.3 % and 10.3 % in the placebo, 12.5 and 25 mg *qd* naloxegol doses. Incidence of abdominal pain, diarrhea, nausea , flatulence and upper abdominal pain increased with active treatment and naloxegol dose across placebo, 12.5 mg and 25 mg *qd* doses respectively. Hyperhidrosis occurred at greater incidence in the 25 mg *qd* dose.

In the phase 3 clinical trial 005, safety findings suggest that the adverse event frequency was higher with the 25 naloxegol dose compared to placebo or 12.5 mg *qd*. These rates were 58.9 %, 59.6 % and 69 % in the placebo, 12.5 mg and 25 mg *qd* doses. There were 5.2 %, 6.1 % and 3.4 % patients with serious adverse events in the placebo, 12.5 mg and 25 mg groups of naloxegol. Percentage discontinuations due to adverse events were 5.2 %, 5.2 % and 10.3 % in the placebo, 12.5 and 25 mg *qd* naloxegol doses. Incidence of abdominal pain, diarrhea, nausea , vomiting, flatulence and upper abdominal pain increased with active treatment and naloxegol dose across placebo, 12.5 mg and 25 mg *qd* doses respectively.

Per the pharmacometrics review, both dose-response and exposure-response relationships were evident for gastrointestinal related adverse events (Table 3 and Figure 7). In particular abdominal pain was evaluated by severity (Figure 8) and exposure-response for adverse events for moderate & severe and severe AEs was considered to be shallow. Dose-response was apparent for discontinuations due to withdrawal events, but the analysis was limited due to the small number of discontinuations due to withdrawal AEs.

Table 3: Dose-response for the number of individuals with all-grade gastrointestinal related adverse events for studies 04 and 05 combined

	Placebo	12.5 mg	25 mg
	N=444	N=441	N=446
Abdominal Pain	25	43	71
Diarrhea	19	25	41
Nausea	20	29	36
Flatulence	11	13	26
Vomiting	13	10	20
Upper Abdominal Pain	7	8	17

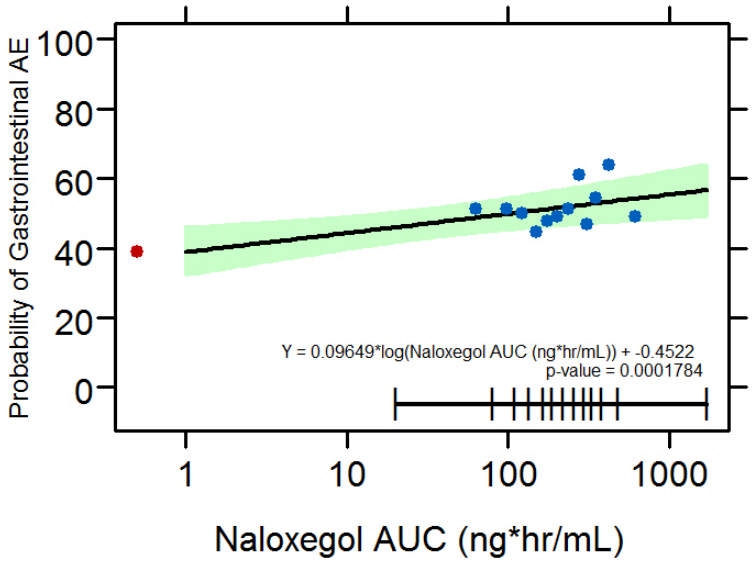


Figure7. Exposure-response is evident for gastrointestinal related adverse events. The logistic regression and prediction interval is shown by the solid line and shaded region. The analysis was conducted on placebo and naloxegol data simultaneously, assuming placebo concentrations of naloxegol were zero. Data points are the probability for the exposure bin, denoted by the bars at the bottom of the plot.

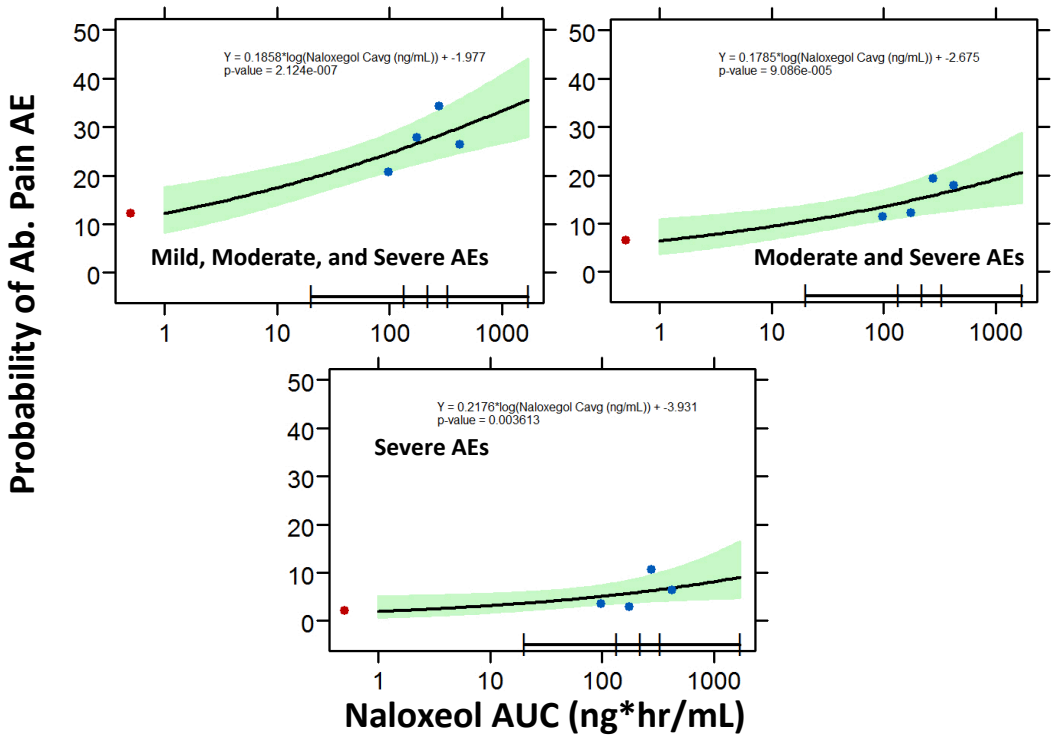


Figure 8. Exposure-response relationships exist for abdominal pain by severity. The logistic regression and prediction interval is shown by the solid line and shaded region. The analysis was conducted on placebo and naloxegol data simultaneously, assuming placebo concentrations of naloxegol were zero. Data points are the probability for the exposure bin, denoted by the bars at the bottom of the plot.

Table 4: Number (%) of patients with preferred terms potentially related to opioid withdrawal during the treatment period (12-week pool of studies 04 and 05 and study 08)

	12-week pool (Studies 04 and 05)			52-week safety study (Study 08)	
	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)	Usual care (N=270)	NGL 25 mg (N=534)
Any PT	27 (6.1)	30 (6.8)	52 (11.7)	36 (13.3)	113 (21.2)
Hyperhidrosis	1 (0.2)	2 (0.5)	13 (2.9)	1 (0.4)	17 (3.2)
Anxiety	5 (1.1)	7 (1.6)	7 (1.6)	4 (1.5)	17 (3.2)
Arthralgia	5 (1.1)	4 (0.9)	5 (1.1)	16 (5.9)	33 (6.2)
Drug withdrawal syndrome	1 (0.2)	2 (0.5)	5 (1.1)	0	2 (0.4)
Hot flush	2 (0.5)	2 (0.5)	4 (0.9)	3 (1.1)	6 (1.1)
Muscle spasms	3 (0.7)	3 (0.7)	3 (0.7)	8 (3.0)	17 (3.2)
Palpitations	1 (0.2)	3 (0.7)	3 (0.7)	1 (0.4)	2 (0.4)
Tremor	2 (0.5)	1 (0.2)	3 (0.7)	1 (0.4)	2 (0.4)
Rhinorrhea	0	1 (0.2)	3 (0.7)	1 (0.4)	4 (0.7)
Myalgia	0	0	3 (0.7)	1 (0.4)	3 (0.6)
Insomnia	3 (0.7)	1 (0.2)	2 (0.4)	5 (1.9)	15 (2.8)
Flushing	1 (0.2)	1 (0.2)	2 (0.4)	0	3 (0.6)
Cold sweat	0	1 (0.2)	2 (0.4)	0	1 (0.2)
Yawning	1 (0.2)	0	2 (0.4)	0	3 (0.6)
Feeling jittery	1 (0.2)	2 (0.5)	1 (0.2)	0	1 (0.2)
Chills	1 (0.2)	1 (0.2)	1 (0.2)	0	11 (2.1)
Restlessness	1 (0.2)	0	0	0	4 (0.7)
Tachycardia	1 (0.2)	0	1 (0.2)	0	3 (0.6)
Sneezing	0	0	0	2 (0.7)	2 (0.4)
Irritability	0	1 (0.2)	1 (0.2)	0	2 (0.4)
Muscle twitching	0	0	0	0	2 (0.4)

(Source: Sponsor's Opioid Withdrawal and CV Risk Assessments Report, Table 1)

Table 5: Number (%) of patients with discontinuations due to AEs potentially related to opioid withdrawal (12-week pool in studies 04 and 05 and Study 08)

	12-week pool (Studies 04 and 05)			52-week safety study (Study 08)	
	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)	Usual care (N=270)	NGL 25 mg (N=534)
Any DAE	**6 (1.4)**	**0**	**9 (2.0)**	**Not applicable[a]**	**10 (1.9)**
Hyperhidrosis	1 (0.2)	0	4 (0.9)		3 (0.6)
Myalgia	0	0	2 (0.4)		1 (0.2)
Drug withdrawal syndrome	1 (0.2)	0	1 (0.2)		0
Yawning	1 (0.2)	0	1 (0.2)		0
Chills	0	0	1 (0.2)		3 (0.6)
Drug effect decreased	0	0	1 (0.2)		0
Feeling jittery	0	0	1 (0.2)		0
Drug dependence	0	0	1 (0.2)		0
Rhinorrhea	0	0	1 (0.2)		0
Night sweats	1 (0.2)	0	0		0
Restlessness	1 (0.2)	0	0		1 (0.2)
Palpitations	1 (0.2)	0	0		0
Tachycardia	1 (0.2)	0	0		0
Tremor	1 (0.2)	0	0		0
Flushing	1 (0.2)	0	0		0
Arthralgia	0	0	0		2 (0.4)
Anxiety	0	0	0		1 (0.2)

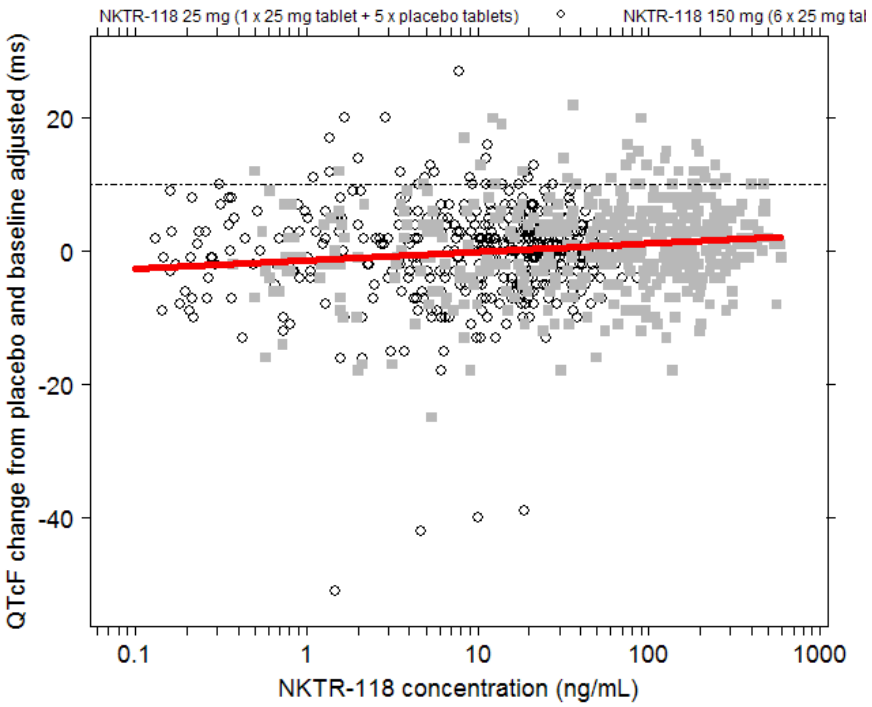
(Source: Sponsor's Opioid Withdrawal and CV Risk Assessments Report, Table 3)

Further details on the exposure-response for safety analysis can be found in the pharmacometrics review in the appendices.

2.2.4.3 Does this drug prolong the QT or QTc interval?

While there appears to be an apparent exposure response relationship for naloxegol effect on the QT interval (**Error! Reference source not found.**), the IRT division concluded:

> "No significant QTc prolongation effect of NKTR-118 was detected in this TQT study. The largest upper bound of the 2-sided 90% CI's for the mean differences between NKTR-118 and placebo is below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI's for the ΔΔQTcF effect for moxifloxacin is greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established."



(Source: IRT review team's report for IND 78781, July 9, 2013)

Figure 9: Apparent exposure response for naloxegol effect on the QT interval prolongation at doses up to 150 mg.

Is there an option of allowing lower dose of 12.5 mg in patients who cannot tolerate the drug due to abdominal pain?

Yes, for patients that cannot tolerate the drug due to abdominal pain, it is recommended to reduce the dose to 12.5 mg prior to discontinuing the drug. In trial 04, the 12.5 mg naloxegol dose was superior to placebo, yet it was numerically lower than 25 mg naloxegol arm. In the replicate trial 05, the primary efficacy response rates for both 12.5 mg naloxegol and 25 mg naloxegol treatment groups were decreased compared to trial 04 for unexplained reasons. Regardless of this decrease in study 05, the 12.5 mg arm is numerically better than placebo and the delta between the 25 mg arm is similar to that in trial 04. Additionally, there is a significant exposure-response relationship (Figure 2) which provides evidence of effectiveness and demonstrates that the response rates for these two doses are not that far apart. While 12.5 may have failed superiority in trial 05, there appears to be an evidence to suggest that patients receiving 12.5 would still benefit over those receiving placebo.

For patients that cannot tolerate the drug due to abdominal pain, it is recommended to reduce the dose to 12.5 mg prior to discontinuing the drug. The following tables and figures show that, in general, patients with abdominal pain show greater response to naloxegol as assessed by both primary (Table 1, Figure 3) and secondary (Table, Figure) efficacy measures.

Table 6: Primary efficacy endpoint shows numerically higher response rate for those patients that experienced abdominal pain AEs compared to those who didn't.

	No Abdominal Pain AE		With Abdominal Pain AE	
Treatment	N	Response Rate (%)	N	Response Rate (%)
Placebo	131/449	29.1	11/32	34.4
NKTR-118 12.5 mg	158/422	37.5	25/56	44.4
NKTR-118 25 mg	163/392	41.6	45/100	44.8

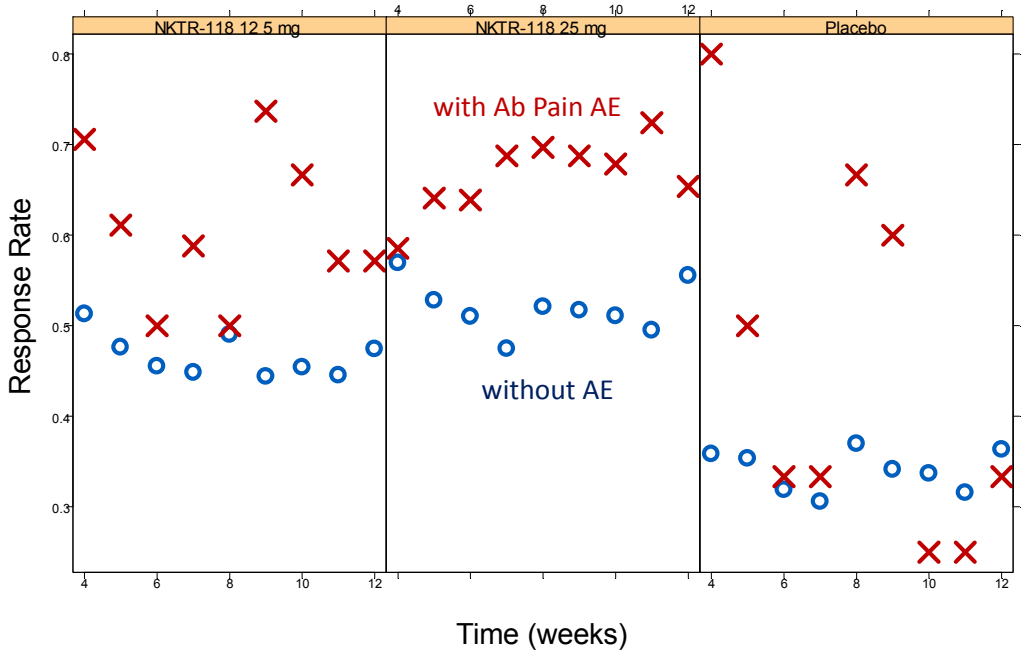


Figure 10: Patients with abdominal pain adverse events appear to have higher response rates compared to those without abdominal pain AEs. Red X and blue circles represent the response rate* for patients with and without abdominal pain AEs, respectively. Data are from studies 04 and 05 combined.

*Response rate was calculated for each week prior to week 12 to mimic the sponsor's primary endpoint at week 12. At each week the patient must have had at least 3 SBMs and an increase of at least 1 from baseline. Additionally ¾ of all their prior weekly evaluations had to result in responder status and for 3 out of the last 4 weekly assessments the patient must have been responding.

The analysis was also performed for two secondary endpoints: 1) time to first post-dose SBM and 2) mean number of days per week where > 1 SBM.

Table 7: Patients with abdominal pain adverse events appeared to exhibit shorter durations to the first post dose SBM. Results are shown as the median for each treatment group for both studies 04 and 05.

	Time to first post-dose SBM (hr)	
Treatment	No Abdominal Pain AE	With Abdominal Pain AE
Placebo	37.5	23.1
NKTR-118 12.5 mg	15.1	3.4
NKTR-118 25 mg	20.8	3.3

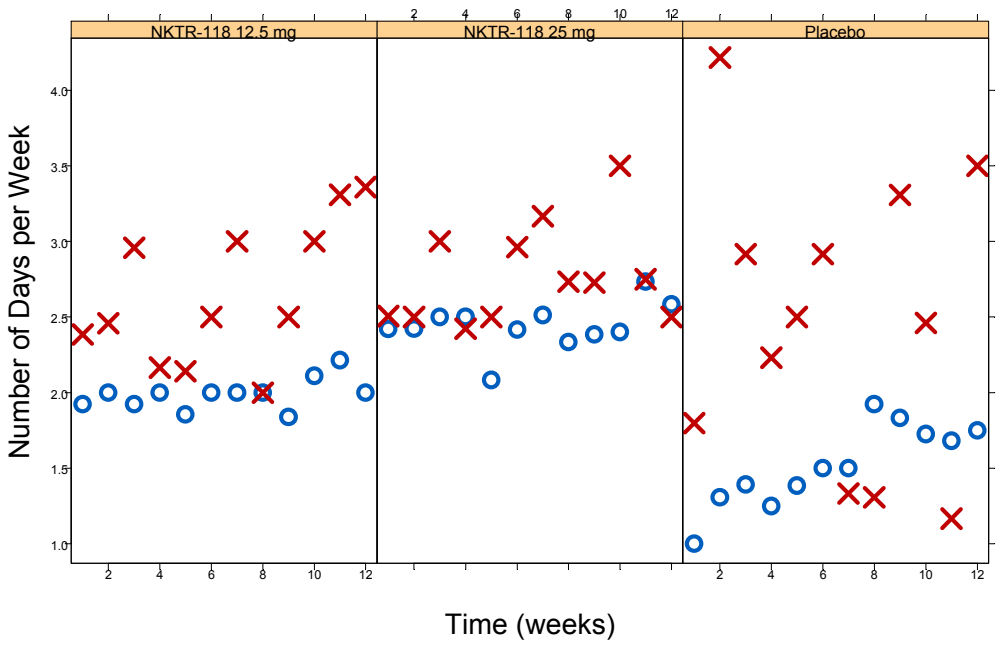


Figure 11. The mean number of days per week where SBMs were greater than 1 appears to be higher for those patients with abdominal pain AEs compared to those without. Red X and blue circles represent the number of days per week where SBMs were > 1 for patients with and without abdominal pain AEs, respectively. Data are from studies 04 and 05 combined.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The sponsor's proposed dose of 25 mg appears reasonable for those that can tolerate it (>85% of patients in phase 3 studies 04 and 05). This dose also appears to offer more benefit over the 12.5 mg dose based on the primary efficacy analysis and on other key secondary end points. However based on the observed shallow dose/exposure-response relationship for efficacy, we recommend that for patients who cannot tolerate the drug due to abdominal pain, dose can be reduced to 12.5 mg prior to discontinuing the drug.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

Single dose pharmacokinetics of naloxegol has been evaluated in several phase 1 trials in healthy volunteers. Multiple dose pharmacokinetics after once daily dose has been evaluated in Phase 2b PK sub-study, in a Japanese PK study and in clinical trials of OIC using sparse sampling. There are several metabolites for naloxegol but none is considered a major metabolite.

2.2.5.1 What are the single dose and multiple dose PK parameters?

The following table summarizes the single dose PK parameters of naloxegol following 25 mg administered to healthy volunteers (representative single dose PK summary from the one of the phase I trials in healthy volunteers):

Table 8: Pharmacokinetics of naloxegol in healthy volunteers (Study D3820C0012)

Arithmetic mean ± S.D. (% CV)	**Naloxegol 25 mg alone (n = 22)**
Tmax (h) Median (range)	1.00 (0.25 – 5.00)

Cmax (ng/mL)	43 ± 18.6 (47 %)
AUC0-24 (ng h/mL)	174 ± 70 (42 %)
AUC0-t (ng h/mL)	178 ± 74 (43 %)
T1/2 (h)	7.6 ± 6.2 (57 %)
Vz/F (L)	1550 ± 822 (53 %)
CL/F (L/h)	163 ± 68 (44 %)

The single and multiple dose PK parameters following a 25 mg *qd* dose for 10 days in healthy young adult Japanese volunteers are summarized below in comparison to the single dose PK information:

Table 9: Single and steady-state PK of naloxegol in Japanese volunteers (Study D3820C00020)

25 mg q.d. naloxegol PK	**Day 1 (n = 6)**	**Day 10 (n = 6)**
Cmax; ng/mL	45 ± 20	54 ± 15
Tmax; h	0.5 [0.5-1.0]	0.5 [0.5-1.0]
AUC0-24; ng h/mL	153 ± 42	161 ± 36
AUC0-t; ng h/mL	156 ± 42	165 ± 39
AUC; ng h/mL	158 ± 42	168 ± 38
AUC0-tau; ng.h/mL	N/A	161 ± 36
T1/2; h	7.7 ± 2.8	9.1 ± 4.1
CL/F; L/h	168 ± 43	162 ± 37
Vz/F; L	1906 ± 949	2098 ± 1027

Plasma naloxegol concentration vs. time curves in healthy young and elderly Japanese volunteers following single and multiple doses are shown; data suggests minimal accumulation after once daily dosing at various dose levels and achievement of steady-state by day 5 based on visual inspection of trough concentrations. Dose-related increases in exposure are noted.

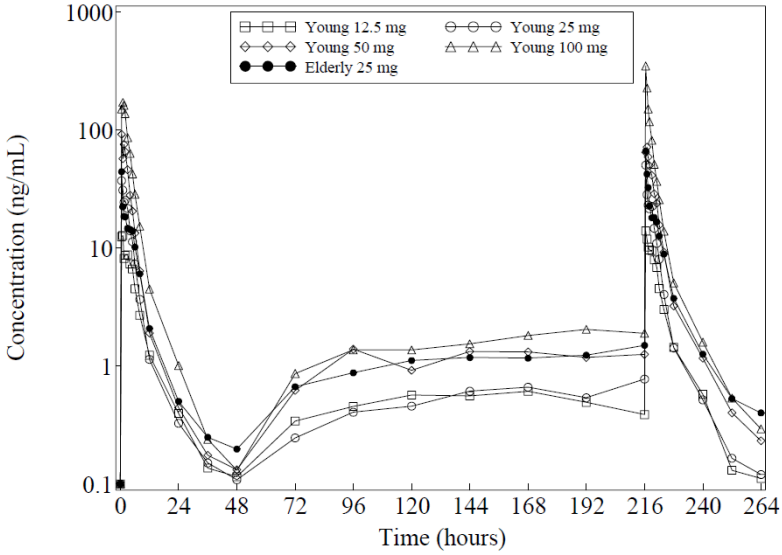


Figure 12: Single and multiple dose pharmacokinetic profiles of naloxegol at various dose levels in young volunteers and in elderly subjects (25 mg); Source: Sponsor's report D3820C00020

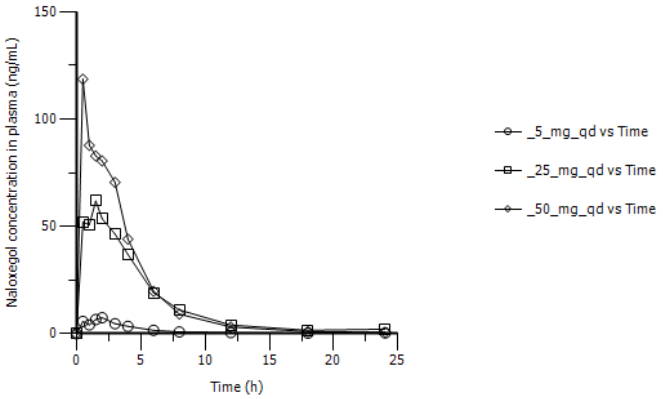
2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The pharmacokinetics of naloxegol, naloxegol glucuronide and naloxone were evaluated in the Phase 2b study in OIC patients with chronic non-cancer pain. Naloxegol PK variability was comparable in healthy volunteers and patients. The mean exposure parameters for naloxegol such as Cmax and AUC in OIC patients in the PK sub-study were similar to those noted in control groups of phase 1 renal and hepatic PK studies which exhibited somewhat higher exposure compared to that noted in healthy volunteers of various PK and DDI studies in the NDA. The reason for this difference is unclear, however sample sizes in the Phase 2b sub-study and control groups of renal and hepatic PK studies tended to be smaller (5-12) compared to sample sizes in the DDI studies of naloxegol (~22-24). T1/2 values for OIC patients were also somewhat longer (at steady-state) compared to a range of 6-11 hours noted in healthy volunteer PK studies of naloxegol. No accumulation was noted after once daily dosing of 25 mg naloxegol in OIC population and while exposures increased with dose, the increase was more than dose proportional from 5 mg *qd* to 25 mg *qd*. The metabolite profile in OIC patients was similar to those in healthy volunteers with multiple, but no major metabolite.

Table 10: Single dose and steady-state PK of naloxegol in OIC patients in Phase 2b PK sub-study

Day	Dose (mg)	N	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{(0-24)}$ (hr*ng/mL)	$T_{1/2}$ (hr)
1	5	5	1.7 (84.7)	9.1 (52.2)	34.01 (48.8)	NC
	25	12	1.5 (61.1)	70.6 (42.3)	327.7 (47.7)	NC
	50	5	1.5 (91.3)	123.7 (36.3)	426.8 (22.1)	NC
28	5	4	1.5 (81.7)	8.0 (49.2)	39.0 (23.1)	17.4 (8.3)
	25	9	1.4 (43.9)	81.1 (45.7)	334.8 (51.4)	14.1 (4.9)
	50	4	1.6 (101.7)	100.0 (41.9)	403.6 (36.7)	20.3 (10.3)

Single dose (day 1) and steady-state (day 28) plasma naloxegol concentration-time profiles from phase 2b patients in the PK sub study are summarized in the plots below:



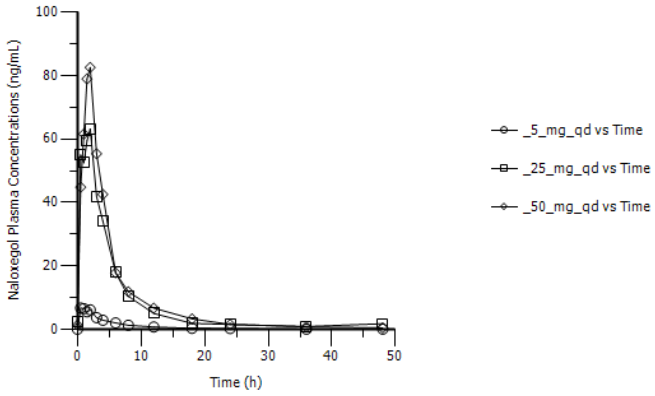


Figure 13: Single and multiple dose PK profiles of naloxegol in patients of phase 2b PK sub-study

2.2.5.3 What are the characteristics of drug absorption?

Following oral administration, naloxegol is found to be absorbed with peak concentrations occurring within 0.5-2 h; majority of individuals, and across a wide dose-range, demonstrated double peaks in the c-t profiles, with the second peak occurring approximately 0.5-3 h after the first. Sponsor suggested that the double peak could be due to entero-hepatic recirculation of the drug; however this has not been conclusively established.

Food increases Cmax and AUC of naloxegol. Plasma concentrations of naloxegol were greater under fed conditions for both the phase III (naloxegol free base; Cmax and AUC higher by 47 % and 55 %, respectively) and commercial (Oxalate; Cmax and AUC higher by 30 % and 46 % respectively) formulation. However, in clinical trials dosing was under fasted conditions. Accordingly, in the proposed labeling, sponsor recommends dosing under fasted conditions. Naloxegol is a substrate of the P-glycoprotein efflux transporter. The absolute bioavailability of naloxegol was not determined.

2.2.5.4 What are the characteristics of drug distribution?

The binding of naloxegol to human plasma proteins, as assessed by equilibrium dialysis at concentrations of 1.5 µM, 15 µM, and 150 µM is low (4.2 %) and generally concentration-independent. The mean apparent volume of distribution during the terminal phase (Vz/F) in healthy volunteers ranged from 968 to 2140 L across dosing groups and studies.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

The mass balance of ^{14}C-naloxegol was evaluated in six healthy male volunteers. Radioactivity recovery data from this study and the subsequent detailed metabolic profiling analyses of the biological samples collected were presented separately as two reports; Overall, data suggest that renal route of elimination is ~ 6-10 %. There were a number of metabolites in feces (predominant route of elimination for the radioactivity) and in the systemic circulation. Along with the findings from in vivo drug-drug interaction, DDI studies, the overall data suggest a significant role for metabolism. A potential contribution of the biliary pathway is suspected although not formally evaluated.

An overview of results from the mass balance and metabolic profiling studies are summarized here;

Study D3820C00001 ('Mass Balance Study') was a phase 1, open-label, single dose study in n= 6 healthy male volunteers (50 -65 years inclusive). Based on urinary recovery of dosed radioactivity, fraction absorbed of oral naloxegol dose appears to be at least 16 %. Together, urine and feces accounted for a mean total cumulative combined recovery of 84.2 % (74.2 % to 93.2 %). Most of the radioactivity was recovered in feces (67.7 %; range: 61.9 – 80.4 %) while ~ 16 % (range: 12.6 – 21.3 %) was recovered in urine. Thus the primary elimination pathway for total radioactivity per the findings of this study was via feces. Unchanged naloxegol recovered in urine was ~ 6 - 10 %. Based on the observed plasma concentrations to whole blood radioactivity ratios, majority of circulating radioactivity in plasma (~ 67 % of AUC) appears to be due to naloxegol metabolites. Lack of significant radioactivity in red blood cells indicates plasma to be an appropriate matrix for naloxegol and metabolite analyses. A 100 % dose recovery was not obtained in any individual in this study; however the range of recovery was 74-93 %.

Cumulative amounts of radioactivity recovered in urine and fecal collections as well as their combined amounts in ngEq are shown in figure and table below:

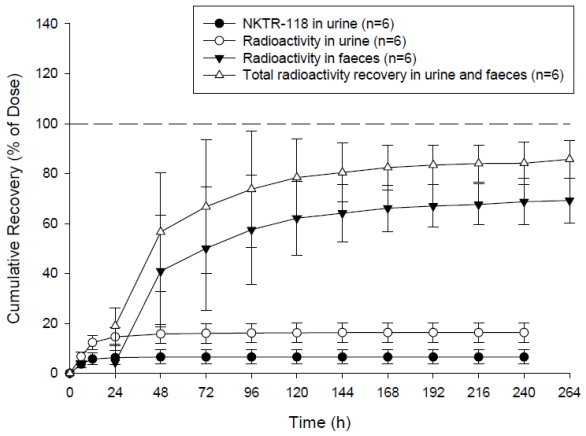


Figure 14: Cumulative % recovery of naloxegol related radioactivity in the mass balance study (source: Sponsor's report D3820C00001)

Table 11: Individual radioactivity recovery data from the mass balance study

	NKTR-118 in Urine		Radioactivity in Urine		Radioactivity in Faeces[a]		Total Radioactivity	
	Dose recovered		Dose recovered		Dose recovered		Dose recovered	
Subject/ Statistic	ng	% dose	ngEq	% dose	ngEq	% dose	ngEq	% dose
E0001001	867000	3.21	3450000	12.8	21700000	80.4	25200000	93.2
E0001017	893000	3.31	3410000	12.6	16800000	62.3	20200000	74.9
E0001018	1860000	6.87	3950000	14.6	20900000	77.4	24900000	92.0
E0001031	2430000	9.01	5700000	21.1	17000000	62.9	22700000	84.1
E0001033	1700000	6.31	4220000	15.6	16700000	61.9	20900000	77.5
E0001037	2750000	10.2	5760000	21.3	17200000	63.8	23000000	85.2
n	6	6	6	6	6	6	6	6
Geometric mean	1590000	5.90	4310000	16.0	18300000	67.7	22700000	84.2
CV%	52.3	52.4	23.8	23.7	12.0	12.0	9.0	8.8
Minimum	867000	3.21	3410000	12.6	16700000	61.9	20200000	74.9
Maximum	2750000	10..2	5760000	21.3	21700000	80.4	25200000	93.2

CV% geometric coefficient of variation in percent; n number of observations.
Note: The table summarises cumulative recoveries over a period of 240 hours postdose for urine and over a period of 360 hours postdose for faeces and total radioactivity.
[a] The collection interval for Volunteer E0001017 was extended to 360 hours. Preceding intervals were used for calculating cumulative excretion (see Section 7.6.1)

Tables below summarize findings from a thorough metabolic profiling of the biological samples collected in the same mass balance study; some discrepancies in recovery values were noted between the primary study conclusions and the data from the metabolic profiling, which were not explained by the sponsor; However, these differences do not significantly alter the conclusions.

During the metabolite profiling of the above samples, naloxegol accounted for the major part of the radioactivity in urine 10% of the dose in healthy volunteers, whereas the major characterized metabolites (M13, M12, M7 and M10) together represented 4% of the dose. One uncharacterized urine metabolite (MX2) represented approximately 2%.

Table 12: Summary of parent and metabolites percentages in urine expressed as fraction of dose

Table 2 Summary of detected metabolites in urine expressed as average fractions of the oral administered dose of [^{14}C]NKTR-118 to healthy volunteers (25 mg, 38.4 µmol, 3.20 MBq)

			[a] Fraction of dose (%)
M#	**[b] Rt (rel. parent)**	**Rt min**	**Healthy male volunteers**
			[c] 0-24h
NKTR-118	1.00	25.1	9.9
MX2[d]	0.68	17.2	1.8
M13	0.70	19.9	1.1
M12	0.80	20.2	0.4
M7	0.83	20.9	0.7
M10	0.85	21.4	1.5
Fraction of dose detected			15.4
Fraction of dose characterised			13.6

[a] The fraction of administered NKTR-118 in urine detected in the radiochromatogram
[b] R_t metabolite/R_t NKTR-118
[c] Collection time after administration
[d] MX denotes uncharacterized metabolite

Within 120 h a mean of 60% of the administered radioactivity was recovered in feces. Five radioactive peaks were characterized which together represented 58% of the dose, including naloxegol which accounted for up to 16% of the dose and four metabolites.

Table 13: Summary of parent and metabolites percentages in feces expressed as fraction of dose

Table 3 Summary of detected metabolites in faeces expressed as average fractions of the oral administered dose of [^{14}C]NKTR-118 to healthy volunteers (25 mg, 38.4 µmol, 3.20 MBq)

			[a] Fraction of dose (%)
M#	**[b] Rt (rel. parent)**	**Rt min**	**Healthy male volunteers**
			[c] 0-120h
NKTR-118	1.00	24.8	16.2
MX1[d]	0.49	12.1	2.2
M13	0.76	18.8	4.5
M12	0.81	20.2	9.1
M10	0.86	21.4	10.9
M1	0.90	22.3	13.7
M4	0.93	23.0	3.8
Fraction of dose detected			60.4
Fraction of dose characterised			58.2

[a] The fraction of administered NKTR-118 in faeces detected in the radiochromatogram
[b] R_t metabolite/R_t NKTR-118
[c] Collection time after administration
[d] MX denotes uncharacterized metabolite

2.2.5.6 What are the characteristics of drug metabolism?

Naloxegol is predominantly metabolized by CYP3A4. The only other enzyme identified *in vitro* in naloxegol metabolism appears to be CYP2D6, the contribution of which to overall metabolism appears to be minor and not likely to be of clinical relevance. Mass balance study indicated at least 6 metabolites which form by partial removal of the pegylated side chain as well as other phase 1 and 2 reactions. Naloxegol glucuronide was below detection in

the systemic circulation at the clinically relevant dose of 25 mg *qd* but was noted at much higher doses. None of the metabolites were present at >10% of the plasma concentrations of parent or drug-related material.

From the samples of the mass balance study D3820C00001, structures of metabolites were determined using mass spectrometrical analyses of the radiochromatographically detected peaks. The plasma metabolites were characterized as partially shortened PEG chain products (M13 and M7) and M7 was further oxidized forming a carboxymethyl group at the end of the PEG chain (M10). Also an N-dealkylation product (M1) was detected in plasma. The urinary metabolites were also partially shortened PEG chain products (M13 and M7) and shortened PEG chain combined with oxidations forming carboxymethyls (M12 and M10). The carboxymethyl group was confirmed by an H/D exchange MS experiment. The major faecal metabolites were an N-dealkylation product (M1) and two carboxymethyl metabolites with different losses of the PEG chain (M12 and M10).

Sponsor claimed that no radiochromatographic peak corresponds to naloxone or naloxol. In response to a request further clarification with regard to this claim, the sponsor provided additional data from mass balance, multiple ascending dose PK, PK analyses of urine samples and in vitro data to support lack of observation of naloxone following naloxegol (oral administration or incubation experiments). Based on the information available, data rules out naloxone concentrations above 0.25 ng/mL (LLOQ for the assay).

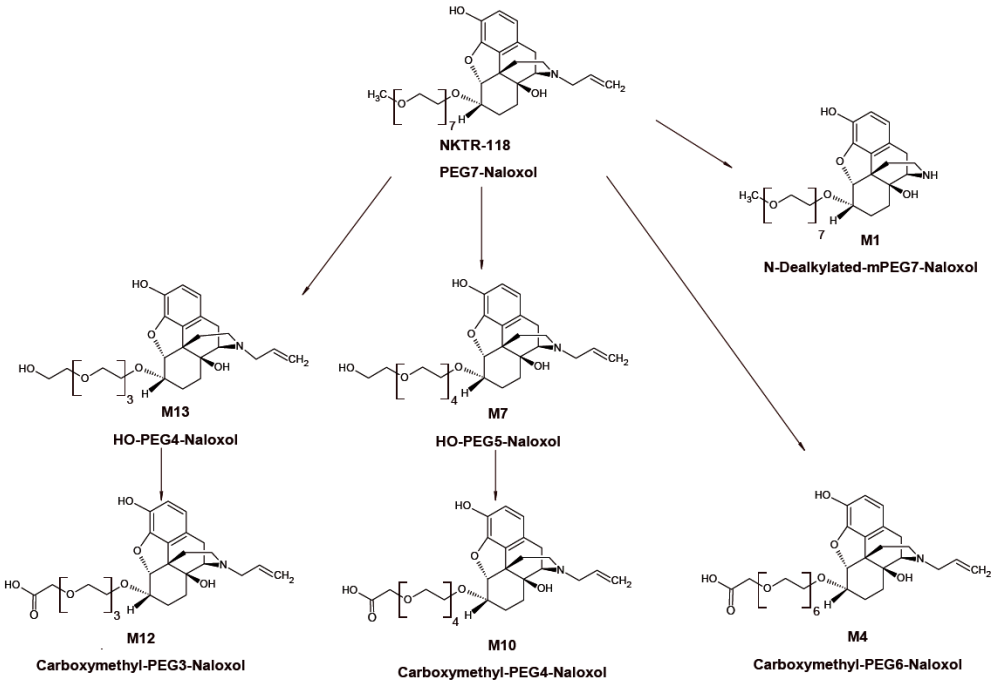


Figure 15: Sponsor's proposed metabolic pathway of NKTR-118 (naloxegol) in man based on the results of the mass balance study (Source: Metabolite profiling report for mass balance study D3820C00001)

2.2.5.7 What are the characteristics of drug excretion?

Renal elimination appears to be a minor pathway (< 10 %) for naloxegol. In the mass balance study, majority of radioactivity in feces (67 %) appeared primarily as metabolites, with 16 % of the radioactivity as unchanged drug. There was presence of significant radioactivity attributable to metabolites in the systemic circulation. This information, and primarily results from various in vivo drug-drug interaction studies, suggests the metabolic pathway to be prominent for naloxegol clearance. In clinical pharmacology studies, the half-life of naloxegol at therapeutic doses ranged from 6 to 11 hours.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Across the range of doses evaluated in phase 1 studies, the area under the plasma concentration-time curve (AUC) increased in a dose-proportional manner; for Cmax, the increases were slightly more than dose-proportional. In general, PK parameters of naloxegol were found to be independent of the dose. Single dose PK data across the dose range from study D3820C00020 are provided below.

Table 14: Single dose PK data across the dose range from study D3820C00020

	12.5 mg	**25 mg**	**50 mg**	**100 mg**
Cmax, ng/mL	19 ± 5	46 ± 20	152 ± 94	375 ± 418
AUC, ng.h/mL	86 ± 33	158 ± 42	371 ± 166	847 ± 483
T1/2, h	7.8 ± 3.14	7.7 ± 2.8	8.0 ± 3.7	6.1 ± 2.4
CL/F, L/h	158 ± 41	168 ± 43	174 ± 110	159 ± 93

2.2.5.9 How do the PK parameters change with time following chronic dosing?

Minimal accumulation based on AUC and some accumulation based on Cmax was noted after once-daily dosing of naloxegol. The accumulation was as expected from single-dose data in young healthy volunteers. The mean accumulation ratio (Rac) (Day 10/ Day 1) was 1.03 to 1.08 based on AUCτ and 0.81 to 1.65 based on Cmax. Steady-state appears to have been achieved within 5 days of daily dosing. PK of naloxegol appear to be in general time-independent (linear). The geometric mean t½λz after multiple dosing appeared prolonged compared to that after single dosing. Sponsor notes that this is probably due to longer sampling period after the last dose on Day 10.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Moderate to high variability was noted in the pharmacokinetics of naloxegol and this was found to be similar in healthy volunteers and in OIC patients, as well after single dose and at steady-state. Sample size, concomitant medications, timing of food intake, concomitant disease status as well as age, are all likely factors that are capable to contributing to PK variability.

Table 15: Naloxegol PK variability across studies in healthy volunteers and patients

% CV data	Pivotal BE Study	Quinidine DDI	Keto DDI	Diltiazem DDI	Rifampin DDI	Hepatic PK Study	Renal PK study	Phase 2b in OIC patients
Cmax	53%	42%	47%	46%	36%	40%	48%	42%
AUC	42%	31%	44%	49%	27%	55%	37%	48%

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

Results from a single and multiple dose PK study in healthy young vs. elderly Japanese volunteers suggests that the Cmax and AUCtau of naloxegol was greater in elderly compared to young subjects by ~ 30 % and 45 % after multiple daily doses of 25 mg naloxegol. Sponsor has not proposed dose adjustment in the elderly. In clinical trials

of naloxegol, geriatric patients constituted roughly 11 % of the study population suggesting that safety and efficacy have been evaluated in this age group. Overall, due to the observed increase in systemic exposure by ~ 45 % in the Japanese study, and increased sensitivity to some medications in this age group, elderly patients should be monitored for tolerability issues following naloxegol.

The PK comparisons (young vs. elderly) at a 25 mg dose of naloxegol in the Japanese study are summarized here briefly:

Following a single 25 mg dose of naloxegol, the arithmetic Cmax and AUC values in elderly were ~ 20-30 % higher compared to younger volunteers at the same dose. T1/2 values were comparable in young vs. elderly.

Following multiple daily dosing of 25 mg *qd*, compared to young healthy Japanese volunteers, Cmax and AUCtau in elderly Japanese volunteers were approximately 44- 54 % greater at steady-state. In elderly volunteers, the T1/2 value at 25 mg dose were greater than that noted for young volunteers at the same dose (12 h vs. 9 h), while CL/F values were somewhat lower compared to young subjects (115 L/h in elderly vs. 162 L/h in young subjects).

Overall CL/F was comparable but more variable after single doses, while steady-state clearance estimate was ~ 30 % lower in the elderly. Renal clearance, CLr values were approximately lower in elderly by 20 % compared to young subjects after single and multiple doses. Accumulation at steady-state was larger as well in elderly ~ 45 % for both Cmax and AUC.

% CV was high in elderly compared to young subjects. Following single doses, variability in Cmax for young vs. elderly was ~ 45 % vs. 60 %, while variability in AUC was ~ 27 % vs. 68 %, respectively. Following multiple doses, % CV for young vs. elderly was ~ 27 % vs. 55 % for $C_{max,ss}$ while it was 22 % vs. 47 % for $AUC_{tau,ss}$.

Table 16: PK differences across young vs. elderly Japanese subjects (25 mg dose)

25 mg dose	**Single dose**		**Steady-state**	
	Young (n = 6)	Elderly (n = 6)	Young (n = 6)	Elderly (n = 6)
Cmax (ng/mL)	45.53 ± 19.51	54.4 ± 32.55	54.13 ± 14.8	78.47 ± 43.22
Tmax (h)	0.5 [0.5 – 1.0]	0.5 [0.5 – 3.0]	0.5 [0.5-1.0]	0.5 [0.5-1.5]
AUC0-t (ng h/mL)	155.6 ± 42.08	202.70 ± 138.23	164.92 ± 39.08	266.90 ± 125.64
AUCtau (ng h/mL)	-	-	161.08 ± 36.16	247.93 ± 116.72
T1/2 (h)	7.69 ± 2.81	7.29 ± 3.38	9.08 ± 4.14	12.08 ± 6.3
CL/F (L/h)	168.18 ± 42.99	165.10 ± 87.75	161.83 ± 36.84	115.28 ± 39.55
Vz/F (L)	1906 ± 949	1525 ± 677	2097 ± 1026	2254 ± 1902
CLr (mL/h)	7629 ± 1047	6266 ± 754	7637 ± 1043	6154 ± 871.2
fe (0-48) %	4.63 ± 1.04	4.85 ± 3.04	4.88 ± 0.79	6.28 ± 2.61
R_{ac}, AUC	-	-	1.12 ± 0.29	1.45 ± 0.48
R_{ac}, Cmax	-	-	1.38 ± 0.78	1.45 ± 0.37

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

Not applicable

2.3.2.3 Gender

Based on PK information from phase 1 and phase 2b data, there doesn't appear to be an effect of gender on naloxegol pharmacokinetics.

2.3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians

PK data following single dose of 25 mg naloxegol in healthy U.S. (African-American and White subjects; Study 0012) vs. Japanese population (Study 0020) suggest modestly higher exposures in Whites compared to the Japanese or African-American population; this was also apparent as lower clearance values in the Caucasian population; However, it is difficult to conclusively comment on PK differences based on the small sample sizes in this cross-study comparison; average PK parameters following a 25 mg single naloxegol oral dose across races are shown:

Table 17: Cross study comparison (Study 0012 in African-Americans and Whites; and Study 0020 in Japanese) of PK data of naloxegol across races

Race	Cmax	Tmax	AUC24	AUC0-t	T1/2	CL/F	Vz/F
Japanese (N = 6)	45.53 ± 19.51	0.66 ± 0.26	152.93 ± 42.29	155.60 ± 42.08	7.69 ± 2.81	168.18 ± 42.99	1906 ± 949
Whites (N = 9)	48.20 ± 22.99	1.69 ± 1.61	185.89 ± 61.95	196.77 ± 70.51	9.79 ± 9.16	144.97 ± 58.74	1714 ± 1115
African-Americans (N = 13)	39.33 ± 14.74	1.83 ± 1.76	165.53 ± 75.56	169.91 ± 78.53	6.05 ± 2.39	175.09 ± 73.53	1436 ± 565

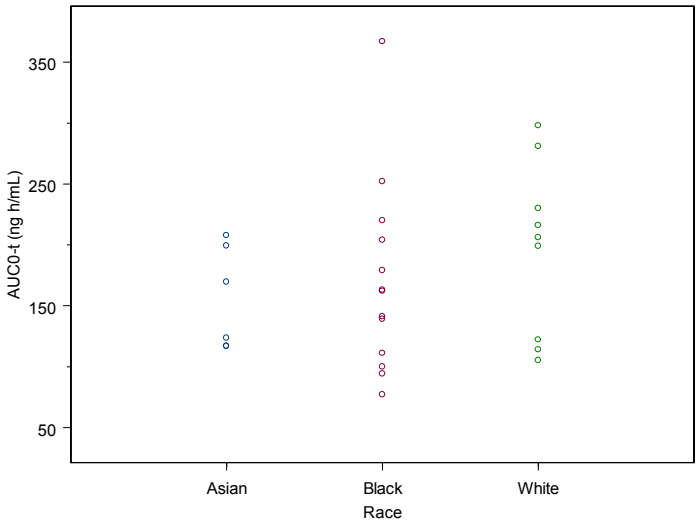


Figure 16: Scatter plot of naloxegol AUC across different race subgroups

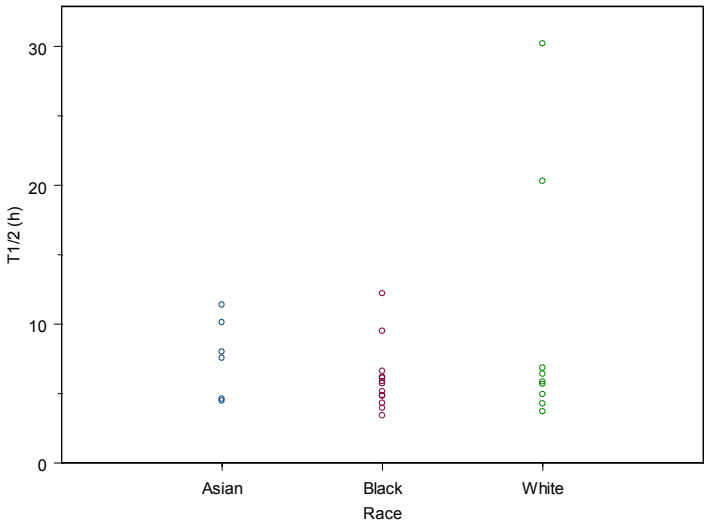


Figure 17: Scatter plot of naloxegol half-life values across different races

2.3.2.5 Renal impairment

- The effect of renal impairment (moderate, severe and ESRD on dialysis) on the pharmacokinetics of naloxegol was evaluated in comparison to a control group.
- Four subjects in the severe group (MDRD) actually had eGFR < 15, thus fitting the criteria for ESRD not yet on dialysis; these four patients on average had approximately 2-fold and 3-fold higher Cmax and AUC compared to control group; however, the high variability and small sample size makes any conclusions difficult for this subgroup;
- ESRD patients on dialysis had systemic exposures comparable to those in normal subjects when dosed 1 to 2 hours before or after hemodialysis. The fraction of dose in dialysate was very minor suggesting that dialysis did not aid in the removal of this drug. Label notes that naloxegol is not dialyzable.
- No significant correlations were noted for eGFR versus exposures (Cmax or AUC), while a significant trend was noted for eGFR vs. overall CL/F.
- Per sponsor's original grouping of the renal subjects, an average of 73 % and 117 % increase in AUC was noted in subjects with moderate and severe renal impairment, respectively compared to normal subjects; In addition the Cmax was increased by 84 % in severe RI patients. High averages were primarily driven by two individuals each in the moderate and severe groups, who individually had 2 - 5 fold higher Cmax values and 3.5-8.4 fold higher AUC values compared to average data in the control group. Clinical characteristics (concomitant diseases, demographics, co-medications etc.) of these individuals with markedly higher exposures were comparable to other study participants. It is likely that these subjects may have experienced higher exposures potentially due to impact of decreased renal function on the metabolism (CYP3A4) or transport (P-gp or other) of the drug at the gut or liver. However, it is unclear as to why renal impairment had a differential effect on these four individuals compared to others in the study; With 25 % of the total subjects with moderate, severe and ESRD renal impairment (4/16), demonstrating higher than normal exposures, it is not possible to dismiss these findings as 'outliers'.

A summary of findings from this renal PK study are provided here:

Scatter plot showing **AUC** values in individuals across renal function groups is shown below; individuals with higher than average values are shown in the groups they appear in;

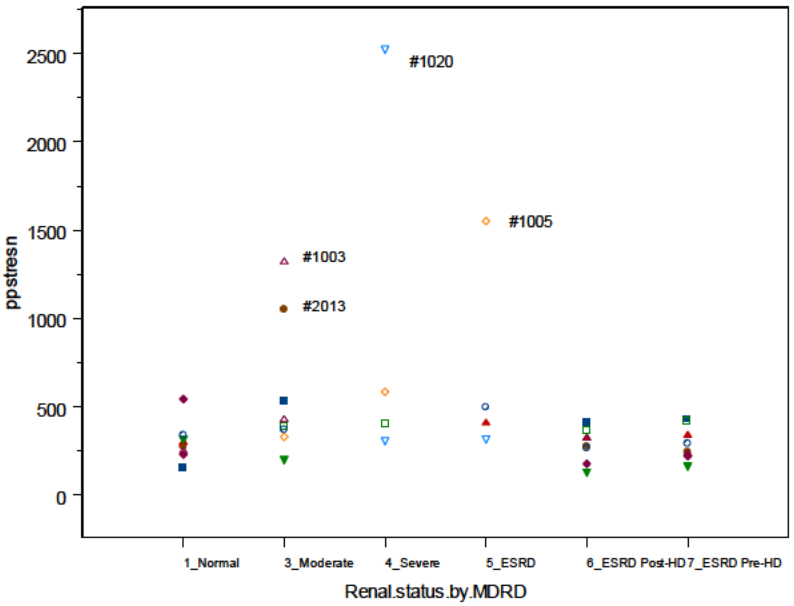


Figure 18: Scatter plot of naloxegol AUC (Y-axis) values across various renal subgroups (Y-axis) with individuals showing markedly higher systemic exposures identified.

- Sponsor has not proposed dose reduction for renal impairment, noting that the majority of patients had systemic exposures similar to those in control group of individuals and that the reasons for the observed higher concentrations ('outliers") in the four individuals couldn't be attributed to any known clinical history characteristics including demographics, disease characteristics or concomitant medication history; instead sponsor has proposed [redacted] (b) (4)
- However, based on the data from this study, it appears reasonable to have a lower starting dose (12.5 mg *qd*) in patients with moderate or worse renal impairment and increase the dose under a physician's guidance if need for additional efficacy has been found and safety has been deemed acceptable. In phase 3 clinical trials, the 12.5 mg *qd* dose was found to be beneficial in OIC although it did not achieve statistical significance in one of the two pivotal trials.

Table 18: Statistical findings for sponsor's original analyses (note that ESRD patients in the table below were on dialysis; Source: NDA report for study D3820C00009)

				Comparison to normal renal function group	
Parameter	**Renal Group[a]**	**N**	**Geometric LS mean**	**Ratio (%)**	**90% CI**
AUC	Normal	6	281.4		
(ng*h/mL)	Moderate	8	487.1	173.06	(101.20, 295.94)
	Severe	8	611.8	217.39	(127.12, 371.76)
	ESRD	8	270.1	95.98	(56.12, 164.13)
C_{max}	Normal	6	80.54		
(ng/mL)	Moderate	8	89.43	111.04	(71.39, 172.71)
	Severe	8	148.2	184.01	(118.31, 286.20)
	ESRD	8	57.18	70.99	(45.64, 110.41)

Reviewer's analysis using geometric mean data separates out the severe as severe and ESRD not yet on dialysis per current guidance; data suggest that compared to normal subjects, patients with moderate, severe and ESRD (not yet on dialysis) had ~ 18 %, 86% and 107 % higher Cmax values and ~ 70 %, 131 %, and 98 % higher AUC;

However, given the unexpectedly higher exposures, it is important to focus on individuals as shown in the scatter plot for AUC, rather than on the mean values for the various renal subgroups;

Table 19: Statistical analyses of PK across renal subgroups (vs. control) in renal PK study 00009

Ratio (%) 90 % CI	Moderate (n = 8)	Severe (n = 4)	ESRD (n = 4)	ESRD Post-HD; (n = 8)	ESRD Pre-HD; (n = 8)
Cmax	118.09 [81 – 175]	186.79 [116- 301]	207.86 [129 – 335]	89.01 [60 – 131]	75.05 [51- 111]
AUCt	170.77 [108-268]	230.99 [132-401]	198.27 [114-344]	94.50 [60 – 148]	98.50 [63 – 155]

2.3.2.6 Hepatic impairment

The effect of mild (Child-Pugh classification A) and moderate (Child-Pugh Classification B) hepatic impairment on the disposition of naloxegol 25 mg was evaluated in comparison with a control group. AUC values in mild to moderate HI subjects were somewhat lower (16- 17 %) based on geometric mean data, while Cmax data was comparable to controls. Effect of severe hepatic impairment (Child-Pugh C) on naloxegol PK was not evaluated.

Sponsor proposes that no dosage adjustment is needed for mild to moderate hepatic impairment. This appears reasonable as no increased exposure was noted. Sponsor also proposes that (b) (4) . It is recommended instead to state in the labeling that (b) (4)

A brief overview of the study results is provided here;

Study D3820C00010 ('Hepatic Impairment PK Study'): A single dose, non-randomized, open-label, parallel group study in a total of 24 subjects (3 groups of 8 each) with normal hepatic function, and mild (C-P A) or moderate (C-P B) HI. Hepatic impairment was assessed based on the patients' Child-Pugh classification.

The mean (±SD) NKTR-118 plasma concentration-time profiles for patients with hepatic impairment and for healthy volunteers with normal hepatic function following single administration of NKTR-118 25 mg white film-coated tablet in a fasted state are presented in the figure below:

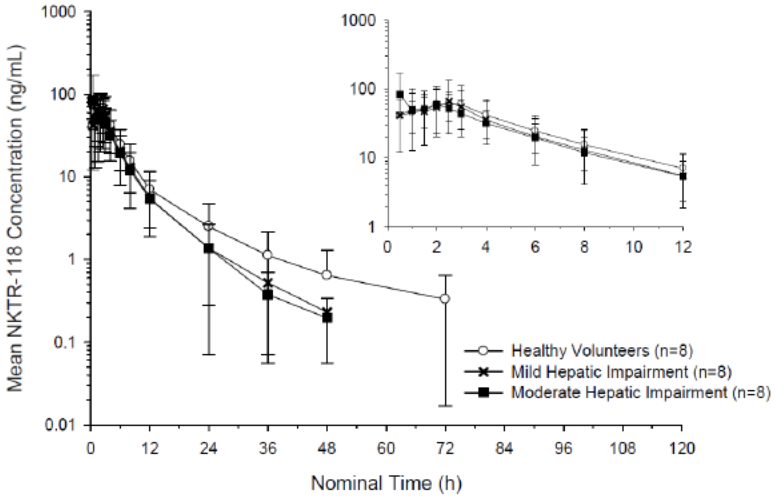


Figure 19: Naloxegol plasma concentration-time profiles in hepatic impairment subjects

Table 20: Statistical analyses of the hepatic PK data by the reviewer

Ratio (%) [90 % CI]	Mild HI (n = 8) C-P A (score 5-6)	Moderate HI (n = 8) C-P B (score 7-9)
Cmax	94.55 [60.4 – 147.9]	99.9 [63.8 – 156.4]
AUC0-t	82.80 [53.7 – 127.6]	82.19 [53.4 – 126.7]
AUCinf	82.86 [53.8 – 127.6]	82.27 [53.3 – 126.7]

The geometric mean ratios for Cmax in both mild and moderate HI groups were close to unity relative to normal subjects; for AUC parameters, the ratios suggest somewhat lower exposures in the mild and moderate HI groups compared to normal subjects. The 90 % CI for Cmax and AUC were clearly outside the standard 80- 125 % bioequivalence criteria (exploratory analyses). Nevertheless, despite an apparent role for metabolism in the clearance of naloxegol, the data do not indicate that hepatic impairment of mild to moderate category increases the systemic exposures of naloxegol following oral administration of clinically relevant 25 mg single dose.

2.3.2.7 What pregnancy and lactation use information is there in the application?

There is no pharmacokinetic or other data from pregnant or lactating females. Sponsor has proposed in the labeling that the use of naloxegol during pregnancy is (b) (4) posing a risk of opioid withdrawal in the fetus.

There is no pharmacokinetic data from the milk of lactating mothers. Sponsor has proposed in the labeling (b) (4) Sponsor notes that in studies using suckling rats naloxegol was excreted in rat milk. Please refer to non-clinical review in this regard.

Are there other human factors that are important to understanding the drug's efficacy and safety?

Addressing the potential for formation of ethylene glycol and diethylene glycol:

The proposed metabolism of naloxegol, a pegylated product, is described as formation of partially shortened PEG chain products. Based on the structures of metabolites provided in the NDA submission, it appears that up to 5 out of the 7 monomers may be released. Sponsor was asked to address the potential for the formation and systemic accumulation of ethylene glycol, diethylene glycol as well as their toxic metabolites such as glycolic acid and oxalic acid as by-products of this metabolism.

In this regard, sponsor notes in their January 28, 2014 response to the agency that "Exposures to EG or DEG that could arise from metabolism of the entire PEG content of a 28.5 mg naloxegol oxalate tablet are low relative to reference doses as shown in Table below. Human metabolism results provided in the naloxegol NDA 204-760 show that complete removal of all PEG content is unlikely to occur; thus, actual exposures are less than that if the entire PEG content was released. EG, DEG or other small molecular weight glycols were not directly measured after naloxegol dose administration. However, if the entire 16.6 mg of PEG in a naloxegol oxalate tablet was fully metabolized to EG, DEG or oxalic acid (OA), the dose levels for these metabolites would still be significantly lower than the dose reported to be safe (reference dose, (RfD), which already includes at least a 100-fold safety margin) as shown in Table below. However, according to the non-clinical reviewer for this NDA Dr. Ng, the reference values utilized by the sponsor are much higher than the ICH PDE values of 6.2 mg.

Table 21: Theoretical maximum dose-to-Reported Safe dose Ratio

Potential Metabolite	Maximum theoretical dose[1] (mg/Kg)	Dose Reported Safe in Humans		Ratio of Theoretical dose-to-Reported Safe dose
		mg/Kg	Type	
Ethylene glycol	0.332	2	RfD[2]	6.0
		15	RfD[3]	45
Diethylene glycol	0.244	1.6	RfD[4]	6.5
Oxalic acid	0.483	3	Average human dietary intake[5]	6.2

1 Maximum theoretical dose if all of the 16.6 mg of PEG in a 28.5 mg naloxegol oxalate tablet was released as the potential metabolite (assumes a 50 Kg human). See appendix 2 for calculated dose based on metabolic profiling. These values estimated from metabolic profiling are significantly lower.
2 IRIS 1989
3 Snellings et al 2013.
4 EC 2008
5 EMA 2003

The sponsor in their response also provided estimations based on observed metabolites which do not suggest complete removal of all monomers during metabolism of naloxegol in humans:

Table 22: Human excreta profiling to estimate the number of PEG monomers released

Table 2 **Human Excreta Profiling – Study SP-D3820-SPE-0530**

Compound	% Dose			# PEG monomers potentially released [1]
	Urine	Feces	Total	
Parent	9.9	16.2	26.1	0
M1		13.7	13.7	0
PEG-alcohol (M7)	0.7		0.7	2
PEG-alcohol (M13)	1.1	4.5	5.6	3
PEG-acids (M4)		3.8	3.8	0
PEG-acids (M10)	1.5	10.9	12.4	2
PEG-acids (M12)	0.4	9.1	9.5	3

1 Based on the structure of the identified metabolite, the number of ethylene glycol sub-units that could theoretically be released is presented.

According to this approach, the administered naloxegol dose was 38.3 µmoles and hence formation of the identified metabolites could potentially release 27.3 µmoles of ethylene glycol (EG), which is equivalent to 1.7 mg per day. In addition, it was concluded that 8% of the dose was not identified in the excreta and 4% was present as components that could not be identified by MS, so assuming the worst case scenario that all the 7-subunits are released as EG for 12% of the dose one can calculate 32.2 µmoles of EG which is equivalent to 2.0 mg per day. This provides a potential maximum of 3.7 mg/day assuming that all the unaccounted for material is released as EG. For a 50Kg human this is equivalent to 0.074 mg/Kg, which is well below the safe recommended dose as discussed above.
The unlikely, but worst case scenario that all EG for the potential maximum exposure calculated above (3.7mg) was then further metabolized to oxalate, would result in 5.37 mg of oxalic acid which is 0.107 mg/Kg of oxalate which is considerably below the average dietary intake.
The administered dose was 38.3 µmoles and hence formation of the identified metabolites could potentially release 10.8 µmoles of diethylene glycol (DEG), which is equivalent to 1.14 mg per day. The unlikely, but worst case scenario that all of the PEG conjugate is released as 3 units of DEG for 12% of the dose, as calculated above, would result in 2.6 mg per day. This gives a potential maximum of 3.8 mg/ per day released as DEG. For a 50 Kg human, this is equivalent to 0.076 mg/Kg, which is below the safe reference dose as discussed above.

Sponsor therefore concludes that "The likelihood that significant amounts of EG, DEG and other toxic metabolites such as OA are formed after naloxegol administration and accumulate to toxic levels after naloxegol administration is low. Even when assuming the worst-case scenario i.e., all PEG in naloxegol was metabolized to EG, DEG, or OA which, based on metabolic profiling is a significant overestimation, the metabolite concentrations after daily dosing would still be below the reported safe or minimally toxic daily doses in humans. None of the toxicities typically associated with EG, DEG or OA were observed in chronic animal studies with substantially higher naloxegol exposures than those in humans at the clinically recommended dose".

Reviewer Comments: Reviewer finds the above argument to be reasonable and recommends that this conclusion should be corroborated against clinical safety findings. The non-clinical reviewers for this NDA, Dr. Yuk-Chow Ng, and Dr. David Joseph (TL) have also reviewed this information. Based upon email correspondence in this regard, Dr. Ng finds the sponsor's estimations based on metabolic profile to be reasonable and that any EG or DEG levels would likely be less than the ICH limits. Please refer to the clinical and non-clinical reviews for further information on this subject.

Formation of naloxone (a centrally acting opioid antagonist) from naloxegol metabolism:

In the 74-day issues letter, the following IR was sent to the sponsor: "We notice that in the mass balance study the ^{14}C-radiolabel is located on the PEG side chain rather than on naloxone moiety. You have noted in your metabolite profiling report that "No radiochromatographic peak corresponds to naloxone or naloxol indicating that, if formed, these would represent less than 1% of unchanged NKTR-118". Given the position of the radiolabel, address how you have ensured that no naloxone has formed during in vivo studies in humans".

In this regard, sponsor has provided the following justification to support their argument that naloxone is not separated during the metabolism of naloxegol:

- In the mass balance study, using positive ion electrospray LC-MS, the theoretical MH+ for naloxol and naloxone were extracted as selected ion chromatograms and contained only background noise. Therefore there was no evidence for the presence of these components. The statement that "if formed, these would represent less than 1%" was included to indicate that the approach had limited sensitivity.
- In the human multiple ascending dose (MAD) study at doses up to 250 mg BID (Study 07-IN-NX002), plasma concentration of naloxone was measured using a validated LC-MS/MS method. Naloxone was only detectable in only 3 of 864 plasma samples at concentrations near the LLOQ of 0.250 ng/ml (concentrations of 0.364, 0.269, and 0.275 ng/ml). Two of these samples were collected predose on day 1 before administration of naloxegol was initiated.
- In report RD00001767, it was concluded that "the formation of naloxol and naloxone after incubation of NKTR-118 with hepatocytes was not observed." In that study, mass spectrum fragmentation information was available from LC-MS examination of standards of both compounds.
- In report RD00001768 it was reported that, using LS-MS/MS methodology, "Naloxone and naloxol were not detected" in human urine samples taken from the MAD study (7-IN-NX002; 250 mg, Day 1, 0-12 h collection).
- Sponsor concludes that the data available show no evidence for the formation of significant levels of Naloxone or Naloxol in vitro or in vivo.

Reviewer comments: In addition to above justification, it is also noted that in the phase2b PK sub-study naloxone was not detected with an LOQ of 0.25 ng/mL. Thus available data supports lack of naloxone > 0.25 ng/mL. However, the LLOQ of the assay employed appears higher compared to other reported values for LC-MS/MS assays of naloxone in literature, some of which have detection limits in pg/mL range. Therefore circulating naloxone concentrations < 0.25 ng/mL cannot be ruled out. It appears that for naloxone challenge tests, IV doses of 0.2 to 0.6 mg naloxone or 0.4 mg IM naloxone are administered to subjects and observed for symptoms such as anxiety, increase in blood pressure, sweating etc. Plasma levels of 0.5 – 2 ng/mL of naloxone are noted with the above indicated doses of IM or IV naloxone. There is lack of information regarding the potential for central effects at concentrations 0.25 ng/mL or below. Therefore, clinical relevance of such concentrations even if detected using an appropriate assay, towards causing central antagonism is unknown. Thus we recommend that the clinical discipline rely upon review of clinical evidence (e.g. withdrawal symptoms, loss of opioid efficacy) in this regard.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

Naloxegol is a substrate of CYP3A4 and P-glycoprotein (P-gp) transporter. Therefore drugs, herbal products or foods that impact these processes, are expected to alter the systemic exposure of naloxegol. In this regard sponsor has conducted in vivo drug-drug interaction studies with strong and moderate CYP3A4/P-gp inhibitors drugs, ketoconazole, and dilitiazem, respectively. In addition, sponsor has evaluated the effect of quinidine, a strong P-gp inhibitor with weak CYP3A4 inhibition, on the pharmacokinetics of naloxegol. The effect of rifampin, an inducer of CYP3A4 and P-gp was also investigated. The results from these drug-drug interaction (DDI) studies in healthy volunteers suggest the following:

1. DDI study with strong CYP3A4/P-gp inhibitor Ketoconazole: Co-administration of naloxegol 25 mg with ketoconazole (400 mg *QD*) resulted in 9.58, 13.00 and 12.85 fold increases in Cmax, AUC0-t and AUC_{inf}, respectively. Sponsor has proposed contraindication of naloxegol co-administration with strong inhibitors of CYP3A4/P-gp. This is reasonable.

2. DDI study with moderate CYP3A4 inhibitor Diltiazem: Co-administration of naloxegol 25 mg with diltiazem XR (240 mg) resulted in a 2.86-fold and 3.41-fold increase in Cmax and AUC of naloxegol. Sponsor has proposed a dose reduction to 12.5 mg *qd* in presence of moderate inhibitors of CYP3A4. Because the increases in exposures with diltiazem (observed) are greater than 2-fold (3.4-fold), OCP recommends avoiding co-administration with diltiazem or other moderate CYP3A4 inhibitors while on naloxegol and if unavoidable, use 12.5 mg qd dose with caution. PBPK simulations with other moderate CYP3A4 inhibitors suggest inhibition mediated increase in naloxegol exposures of up to 5-fold.
3. DDI study with P-gp inhibitor Quinidine: Co-administration of naloxegol 25 mg with quindine, 600 mg resulted in a 2.4-fold increase in Cmax, and 1.4-fold increase in the AUC parameters of naloxegol. In the proposed labeling, sponsor has recommended the following: (b) (4) (b) (4) (b) (4) This appears reasonable based on the data from the completed drug-drug interaction studies with enzyme inhibitors.
4. DDI study with strong CYP3A4/P-gp inducer Rifampin: Co-administration of naloxegol 25 mg with rifampin (600 mg *QD*) resulted in an overall decrease in the Cmax, AUCinf of naloxegol by 76 % and 89 %, respectively. Sponsor proposed labeling notes that use of naloxegol with strong CYP3A4 inducers is not recommended. This appears reasonable due to the potential lack of therapeutic benefit to patients in this scenario.
5. PBPK simulations using moderate CYP3A4 inducer efavirenz suggest a 50 % reduction in naloxegol exposure; therefore use of a 25 mg qd typical dose should be acceptable in presence of drugs that are moderate inducers of CYP3A4. Please see PBPK memo in the appendices for further details in this regard.
6. Sponsor has not formally evaluated the effect of grapefruit juice on naloxegol pharmacokinetics. However, the proposed labeling recommends avoiding use of naloxegol with grapefruit juice; this is acceptable considering the variable and sometimes marked inhibitory effect of grapefruit juice on the PK of drugs cleared by CYP3A4 enzyme.
7. Sponsor has proposed that no dose adjustment is needed with weak inhibitors of CYP3A4. This appears reasonable, considering the data from strong and weak inhibitors as well as quinidine which is also a weak inhibitor of CYP3A4. PBPK simulations support lack of significant exposure changes in presence of weak CYP3A4 inhibitors.

A brief overview for each of the studies above is provided here:

Study D3820C00012 ('Ketoconazole DDI study'): This was an open-label, non-randomized, fixed sequence study in 22 healthy men and women 18- 55 years of age. Volunteers received a single dose of 25 mg naloxegol on day 1 (treatment A), followed by a 2-day washout. Volunteers then received oral doses of 400 mg ketoconazole once daily on the mornings of days 4 to 8 (5 days) (Treatment B); on day 7, 25 mg naloxegol was co-administered with ketoconazole (Treatment C). Drug was administered in the morning under fasted condition. Study results are summarized:

Arithmetic mean concentrations versus time plots for treatment A (drug alone) and treatment C (drug with ketoconazole) indicate a dramatic increase in plasma concentrations of naloxegol (NKTR-118) following co-administration with ketoconazole.

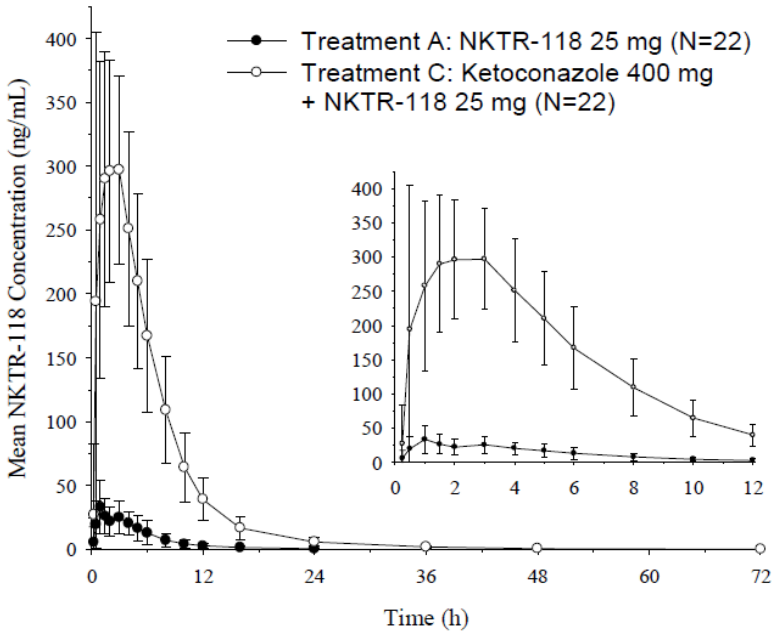


Figure 20: Naloxegol plasma concentration-time profiles in with or without ketoconazole (source: NDA study report D3820C000012)

Table 23: Statistical analyses using geometric mean data are presented below

N = 22	Treatment	Geometric LS mean	Ratio % (C/A)	90 % CI
Cmax (ng/mL)	Naloxegol (A)	39.23	957.67	809.6 – 1132.8
	With Keto (C)	375.7		
AUC0-24 (ng h/mL)	Naloxegol (A)	161.2	1289.44	1141.9 – 1456
	With Keto (C)	2079		
AUC0-t (ng h/mL)	Naloxegol (A)	164.5	1300.07	1144.8–1476.4
	With Keto (C)	2138		
AUCinf (n h/mL)	Naloxegol (A)	166.8	1285.44	1130.6–1461.4
	With Keto (C)	2144		

The fold increases for Cmax, AUC0-t and AUCinf in presence of ketoconazole were 9.58, 13.00 and 12.85 fold, respectively. For all parameters, the mean ratios and 90 % CI intervals were completely outside the pre-specified bioequivalence range. The significant increase in Cmax and AUC parameters as well as the decreased clearance in presence of ketoconazole suggests impairment of systemic CYP3A4 mediated metabolism of naloxegol. The increase in exposure could also be due to inhibition of gut CYP3A4, and P-gp efflux transporter thus increasing intestinal absorption and overall bioavailability when co-administered with ketoconazole.

Study D3820C00032 ('Diltiazem DDI Study'): This was an open-label, non-randomized, fixed-sequence study to assess the effect of diltiazem XR on the PK of naloxegol in n = 43 healthy volunteers. A single dose of 25 mg naloxegol was administered on Day 1 (Treatment A) followed by a 2-day washout (Days 2 and 3). Once-daily doses of 240-mg diltiazem XR were administered on Days 4 through 6 (Treatment B). Co-administration of 25 mg naloxegol with 240 mg diltiazem XR occurred on Day 7 with an additional dose of 240 mg diltiazem XR administered on Day 8 (Treatment C). Volunteers were required to fast from 10 hours before until 4 hours after investigational product (IP) administration on Day 1 and Day 7.

The mean plasma concentration-time profiles of naloxegol with and without Diltiazem show higher concentrations of naloxegol in presence of diltiazem:

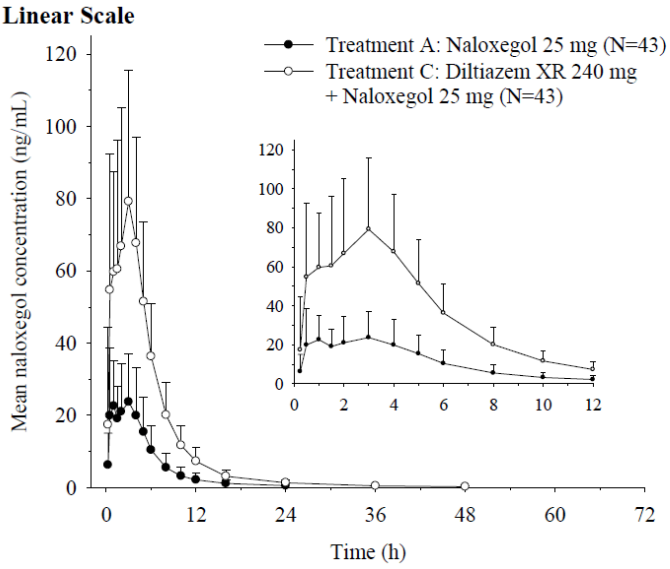


Figure 21: Naloxegol concentration-time profiles with or without diltiazem (source: D3820C00032)

The 90 % CI ratios were extended well beyond the pre-specified no effect upper bound suggesting a significant impact of diltiazem on naloxegol PK:

Table 24: Statistical analyses of naloxegol drug-drug interaction with diltiazem (moderate CYP3A4 inhibitor drug)

N = 43;	Ratio %	90 % CI
Cmax (ng/mL	285.74	(259.48 – 314.66)
AUC0-t (ng/h/mL)	344.28	(318.63 – 371.98)
AUC0-inf (ng.h/mL)	341.29	(316.00 – 368.60)

Study D3820C00011 ('Quinidine DDI study'): This was a double-blind (with regard to quinidine administration), randomized, 2-part, crossover, single-center study in n = 36 male and female healthy volunteers between ages 18- 55 years inclusive. The study consisted of 2 parts, each of which comprised 2 periods. In Part 1 on Day 1 of Period 1, volunteers received a single oral dose of naloxegol 25 mg and quinidine placebo (Treatment A) or NKTR-118 25 mg and quinidine 600 mg (Treatment B). Following at least a 7-day washout period, volunteers received the alternate treatment on Day 1 of Period 2. The treatment sequences for Part 1 were AB or BA. Naloxegol and quinidine were administered via oral route under fasted condition.

Arithmetic mean plasma-concentration time profiles of NKTR-118 with and without quinidine (a strong inhibitor of P-gp) are shown below; Coadministration of quinidine resulted in higher mean naloxegol plasma concentrations initially, followed by rapid decline of naloxegol concentrations:

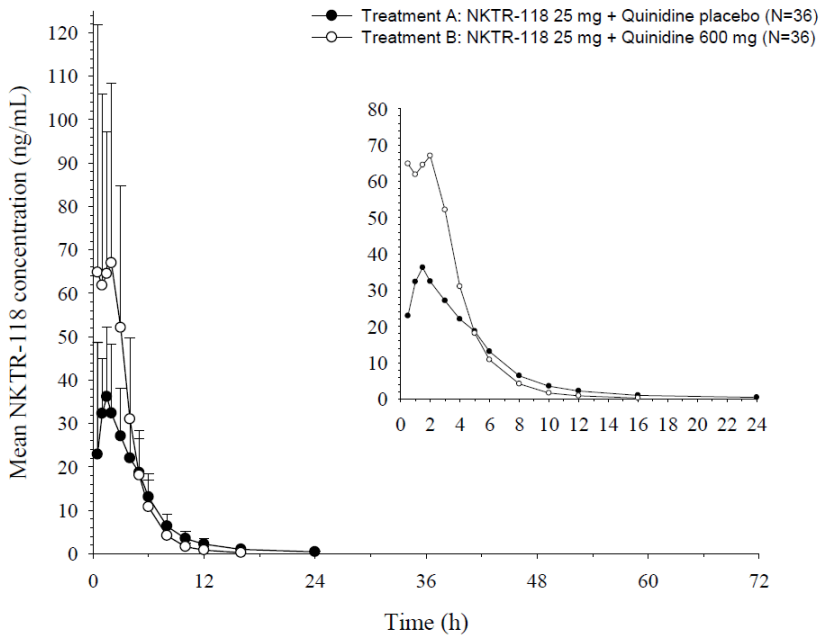


Figure 22: Naloxegol plasma concentration-time profiles with or without quinidine, a P-gp inhibitor (source: Study report D3820C00011)

Statistical comparisons of naloxegol alone vs. naloxegol with Quinidine suggest that the 90 % CI bounds were clearly outside the pre-specified no-effect bounds for all parameters:

Table 25: Statistical comparisons of naloxegol exposures with and without P-gp inhibitor drug

						Comparisons		
Part	**Parameter**	**Trt [a]**	**n**	**Geometric LS mean**	**95% CI**	**Pair**	**Ratio (%)**	**90% CI**
1	AUC	A	36	185.9	(168.2, 205.5)	B/A	138.72	(131.37, 146.48)
	(ng·h/mL)	B	34	257.9	(233.1, 285.3)			
	$AUC_{(0-t)}$	A	36	183.6	(166.2, 202.8)	B/A	141.29	(133.62, 149.39)
	(ng·h/mL)	B	36	259.4	(234.9, 286.5)			
	$AUC_{(0-24)}$	A	35	181.9	(163.8, 202.0)	B/A	163.17	(148.30, 179.53)
	(ng·h/mL)	B	12	296.8	(258.9, 340.1)			
	C_{max}	A	36	43.45	(38.26, 49.36)	B/A	246.61	(219.10, 277.57)
	(ng/mL)	B	36	107.2	(94.36, 121.7)			

Study D3820C00015 ('Rifampin DDI Study'): This was an open-label, fixed-sequence, 3-period, 3-treatment, crossover study to assess the effects of rifampin on the PK of NKTR-118 in healthy volunteers (n =22). On Day 1, volunteers received a single oral dose of 25-mg NKTR-118 followed by a 2-day washout (Days 2 and 3). Volunteers received oral doses of 600-mg rifampin once daily for 10 days on the mornings of Days 4 through 12. On Day 13, 25-mg NKTR-118 was co-administered with 600-mg rifampin.

The mean plasma concentration-time profiles for naloxegol with or without CYP3A4 inducer rifampin are shown below; plasma concentrations decreased markedly in presence of rifampin;

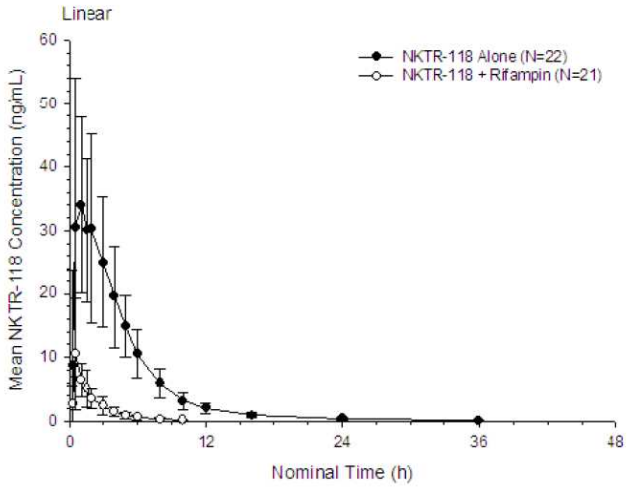


Figure 23: Naloxegol plasma concentration-time profiles with or without rifampin (D3820C00015)

The point estimates of the geometric LS mean ratios and associated 90% CIs for the naloxegol primary PK parameters, AUC and Cmax and an additional partial AUC(0-8) are summarized below; data suggests a statistically significant effect of rifampin on naloxegol PK. Overall, the decrease in naloxegol Cmax, AUC, AUC0-8 in presence of rifampin were 76 %, 89 %, and 87 % respectively.

Table 26: Statistical analyses of naloxegol exposures for the rifampin DDI study

					Comparisons		
Parameter	**Treatment[a]**	**n**	**Geometric LS mean**	**95% CI**	**Pair**	**Ratio (%)**	**90% CI**
AUC	A	22	171.8	(153.2, 192.6)			
(ng·h/mL)	C	21	18.72	(16.65, 21.05)	C/A	10.90	(9.54%, 12.45%)
C_{max}	A	22	45.20	(37.61, 54.32)			
(ng/mL)	C	21	11.06	(9.160, 13.36)	C/A	24.47	(19.63%, 30.51%)
$AUC_{(0-8)}$[b]	A	22	142.6	(127.1, 160.0)			
(ng·h/mL)	C	21	17.93	(15.94, 20.17)	C/A	12.57	(11.01%, 14.36%)

[a] Treatment A: 25-mg NKTR-118 on Day 1.
Treatment C: 600-mg rifampin plus 25-mg NKTR-118 on Day 13
[b] $AUC_{(0-8)}$ was an additional PK parameter added to the analysis.

Data suggests that in presence of strong CYP3A4/P-gp inducer drug rifampin, both Cmax and AUC of naloxegol, a substrate of both CYP3A4 and P-gp were markedly reduced. The clearance of naloxegol was markedly higher likely due to induction of CYP3A4 mediated gut and systemic metabolism as well as increased efflux by P-gp transporter at the gut and/or biliary level. The half-life value of naloxegol was also markedly reduced in presence of rifampin.

Study 05-IN-OX001 (Naloxegol-Morphine PK/PD): This study evaluated the PD (effects of naloxegol on morphine-induced miosis and prolongation of orocecal transit time) and PK of naloxegol, naloxegol glucuronide, as well as the PK of morphine and its glucuronide metabolites following coadministration of morphine (1-minute i.v. infusion of 5 mg/70 kg morphine) with various oral (solution) doses of naloxegol (8, 15, 30, 60, 125, 250, 500, or 1000 mg).

PD information suggested lack of effect of naloxegol on the change from baseline in morphine-induced pupillary constriction (miosis). The peripheral effect of naloxegol was assessed by change from baseline in orocecal transit time, which was not robust enough to draw definitive conclusions.

PK data presented by the sponsor however suggests lack of an effect of naloxegol on the PK of morphine and its metabolites:

Mean plasma concentration-time profiles for morphine and metabolites pooled across dose cohorts were essentially superimposable, independent of treatment, as shown in the following figure.

Mean plasma concentration-time profiles for morphine and metabolites pooled across dose cohorts were essentially superimposable, independent of treatment, as shown in the following figure.

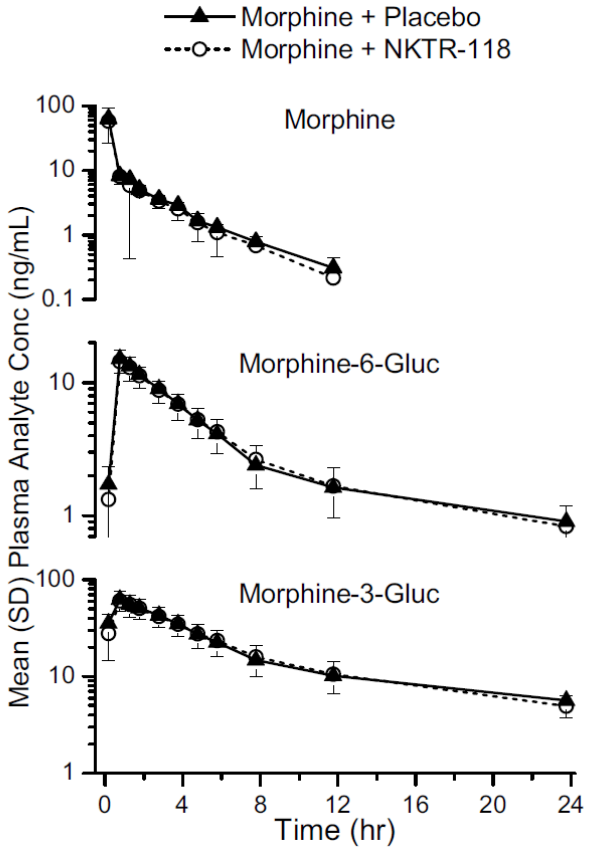


Figure 24: Plasma concentration-time profiles of morphine and its metabolites with or without naloxegol

The 90% CIs for Morphine+NKTR-118 (naloxegol) to Morphine+Placebo ratios for Cmax, AUC(0-last), and AUC(0-inf) values for all analytes were within the 80% to 125% interval used to determine bioequivalence, except the lower 90% CI limit for morphine Cmax was 78.4%:

Table 27: Statistical Analysis of Log-Transformed Pharmacokinetic Parameters for Morphine

Log Transformed	Contrast	Ratio (%)	pvalue	Power	90% Confidence Interval	
					Lower	Upper
C_{max}	Morphine+NKTR-118/ Morphine+Placebo	92.8	0.464	0.699	78.3	110.0
$AUC_{(0\text{-last})}$	Morphine+NKTR-118/ Morphine+Placebo	90.8	0.099	0.984	82.5	100.0
$AUC_{(0\text{-inf})}$	Morphine+NKTR-118/ Morphine+Placebo	91.2	0.105	0.988	83.1	100.1

Data rules out a clinically relevant effect of naloxegol on the pharmacokinetics of concomitant morphine.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Naloxegol is mainly metabolized by CYP3A4/5. It is also a human P-gp substrate. Therefore drugs that impact these enzyme/transporter systems have a potential to alter systemic exposures of naloxegol.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

CYP3A appears to be the major isoform for the metabolism of naloxegol, while CYP2D6 appears to have a minor contribution to the formation of M9. The conclusions were based on studies described below:

Study 1: Study LS-2007-063 assessed metabolism of naloxegol (100 pmol/mL) by six CYP450 enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP2C8) at a protein concentration of 100 pmol/mL using Bactosomes™ containing control (no CYP450 present) and cDNA expressed human CYP enzyme preparations co-expressed with human NADPH CYP reductase. The model substrates are: ethoxycoumarin for CYP1A2, diclofenac for CYP2C9, diazepam for CYP2C19, dextromethorphan for CYP2D6, testosterone for CYP3A4 and amodiaquine for CYP2C8. Each compound was incubated for 0, 5, 15, 30 and 45 min with each isoform. The reactions were stopped by the addition of 50 µL methanol.

The results showed that naloxegol was metabolized extensively in the presence of CYP3A4. The mean (SD) percent of parent remaining following incubation with CYP3A4 was 3.21% (0.392) at 45 minutes versus 56.5% (3.91) at 5 minutes. Naloxegol was metabolically stable in the presence of CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP2C8 Bactosomes™.

Study 2: Study NKTR118DMX3 assessed NADPH dependent cytochrome P450 and FMO enzymes responsible for the metabolism of naloxegol. Two in vitro systems were used: 1) the human liver microsomes (HLM) pooled from 33 human liver donors; and 2) human cDNA expressed enzymes prepared from insect cells infected with recombinant baculovirus containing a cDNA insert for individual human CYP and flavin monooxygenases (FMO) enzymes.

Study using HLM system: Experiments were conducted in HLM to determine the time linearity, protein linearity, and enzyme kinetics. Peak area responses of seven metabolites (N-despropylene NKTR-118 (M1), hydroxyl PEG6 naloxol (M6), hydroxyl PEG5 naloxol (M7), O-desmethyl NKTR-118 (M9), hydroxyl PEG4 naloxol (M13), hydroxyl PEG3 naloxol (M17), and hydroxyl PEG2 naloxol (M44)) were monitored but no authentic standards were available for these metabolites.

The formations of 7 naloxegol metabolites were linear at least up to 20 minutes in HLM system.

The formations of 6 naloxegol metabolites (M6, M7, M9, M13, M17, and M44) were linear up to at least 0.6 mg/mL of HLM protein. M1was identified as a contaminant in the batch of [^{14}C]naloxegol used. Further formation of M1 vs. control was observed, but appears not to be linear over the same protein concentration range as the other metabolites of interest. Based on these results, the enzyme kinetics experiment (see below) was carried out at 0.4 mg/mL human microsomal protein to ensure metabolite formation was in a linear protein concentration range and that sufficient amounts of metabolites would be formed to detect them with adequate accuracy and precision.

Enzyme kinetics
To determine the enzyme kinetics (Km), naloxegol was incubated in triplicate at 0.5, 1, 3, 10, 30, 50, 75, and 100 µM final concentrations with HLM (0.4 mg/mL) at 37°C in a shaking water bath contained incubation mixtures (0.1 M potassium phosphate (pH 7.4), 5 mM MgCl2, and 1 mM NADPH in a total volume of 200 µL). Reactions were terminated at 60 minutes by the addition of 400 µL of acetonitrile.

The apparent Km of 7 metabolites of naloxegol in HLM appeared to follow Michaelis-Menten kinetics for one enzyme. The apparent Km values were in the same order of magnitude (ranging from 22 to 59 µM) for the seven metabolites.

Study using recombinant expressed human CYP and FMO enzymes

[^{14}C]naloxegol (5μM) was incubated in triplicate with microsomes expressing human CYP450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5) at 50 pmol/mL protein. Naloxegol was also incubated with microsomes expressing human FMOs (FMO1, FMO3, and FMO5) at 125 μg/mL. All P450 and FMO incubations were conducted at 37°C in a shaking water bath contained incubation mixtures (0.1 M potassium phosphate (pH 7.4), 5 mM MgCl2, and 1 mM NADPH). Reactions were terminated after 45 minutes by the addition of 400 μL of acetonitrile. Samples were analyzed by HPLC/MS. The formation of 7 metabolites in the presence of individual CYP and FMO were compared to the formation in vector-control Sf9 membranes.

Chemical inhibition studies to confirm the role of the various CYP and FMO enzymes were not performed due to the low levels of the many metabolites observed and unavailability of authentic metabolite standards. Positive control incubations for the various CYP and FMO enzymes were also not performed. As such, the study results are viewed with reservation.

CYP3A4 and CYP3A5 appear to be the major isoforms for the metabolism of naloxegol, while CYP2D6 appears to have minor contributions to the formation of M9. FMO enzymes appeared to have no contribution to the metabolism of naloxegol.

Metabolite profiling
Extracts from a representative HLM incubation with naloxegol (10 μM) in the Study using HLM system and extracts from a CYP3A4 incubation with naloxegol (4 μM) in the study using recombinant were analyzed for radioactivity using off line LSC analysis of fraction collected LC eluates with a TopCount® NXT™ microplate scintillation counter (TopCount) for metabolite profiling.

Based on the peak area responses, naloxegol accounted for 80% and 24% of the total radioactivity in the HLM and CYP3A4 incubation extracts, respectively. No other peaks in the HLM incubations accounted for more than 3% of the total radioactivity. All 7 of the metabolites studied in the HLM kinetic experiments were accounted for in the CYP3A4 incubations, but to greater extents. Additional metabolites found in the CYP3A4 incubation were not observed in significant quantities in HLM. These likely represent further oxidations or combinations of metabolic pathways such as N-dealkylation and cleavage of the polyethylene glycol side chain. CYP3A4/5 enzymes are responsible for metabolism of naloxegol to its metabolites, M1, M6, M7, M9, M13, M17, and M44.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Induction potential
Naloxegol does not have induction potential for CYP1A2, CYP2B6, and CYP3A4 at concentration up to 16 μM (10432 ng/mL), which is much higher than the Cmax (~50 ng/mL) observed in patients. The conclusions were based on two studies described below:

The induction potential was assessed in two in vitro studies with two different cell systems: fresh human hepatocytes and primary cultures of human hepatocytes.

Study 1: Study LS-2007-073 assessed the induction potential of CYP1A2 and CYP3A4 by naloxegol in fresh human hepatocytes. Naloxegol was incubated at three concentrations, 0.1 μM, 1 μM and 10 μM over a 72-hour exposure period with fresh human hepatocytes (n=3 donors). At the end of the 72-hour exposure period, the medium was replaced with CYP-specific probe substrate and incubated for a specific duration. Probe substrates are: ethoxyresorufin for CYP1A2 (20 mM), midazolam (20 μM) for CYP3A4. Dexamethasone (50 μM) and rifampicin (10 μM) were the control inducers for CYP3A4, and omeprazole (50 μM) was the control inducer for CYP1A2. Negative control for the positive control inducers consisted of culture medium containing 0.1% DMSO. Increases in enzyme activity that were ≥ 40% of the respective positive controls were considered an indication of induction.

The results are shown in the table below. All positive control inducers performed as expected. Naloxegol did not cause any significant induction of CYP1A2 or CYP3A4 activity in any of the three individual donors assessed.

Table 28: In vitro assessment of enzyme induction potential of naloxegol

LS-2007-073 CYP1A2

NKTR-118 concentration (µM)	Mean induction (fold increase)		
	Donor 1	Donor 2	Donor 3
0.1	1.18	1.15	1.00
1	1.14	1.04	0.98
10	1.02	1.08	1.03
Omeprazole (50 µM)	20.5	6.57	11.5

LS-2007-073 CYP3A4

NKTR-118 concentration (µM)	Mean induction (fold increase)		
	Donor 1	Donor 2	Donor 3
0.1	1.41	1.06	0.91
1	1.85	0.86	0.87
10	1.11	0.75*	0.64*
Dexamethasone (50 µM)	3.52	5.78	14.8
Rifampicin (10 µM)	7.58	17.0	26.7

* statistically significantly lower than control

Study 2: Study 00003CYP_IND_HHEP assessed the induction potential of CYP1A2, CYP2B6 and CYP3A4 by naloxegol in primary cultures of human hepatocytes. Naloxegol was incubated in preparations of human hepatocyte cultures prepared from cryopreserved hepatocytes (n=3 donors) at concentrations of 0.1, 0.2, 0.6, 1.8, 5.3 and 16 µM. Hepatocytes were also incubated with six concentrations of positive control inducing agents, omeprazole (0.21-50 µM) for CYP1A1/2, phenobarbital (8.2-2000 µM) for CYP2B6, 6-(4-Chlorophenyl) imidazo[2,1-b][1,3]thiazole-5-carbaldehyde O-(3,4-dichlorobenzyl)oxime (CITCO) (0.0041-1 µM) for CYP2B6 and rifampicin (0.040-10 µM) for CYP3A4/5. After 2 days of exposure, enzyme induction was determined by *in situ* catalytic activity assays selected for each CYP enzyme. The probe substrates are: Phenacetin (100 µM) for CYP1A1/2, Bupropion (250 µM) for CYP2B6, and testosterone (200 µM) for CYP3A4/5. In addition, mRNA expression levels of these drug-metabolizing enzymes were evaluated.
The results are shown in the table below. All positive control inducers performed as expected. Treatment with naloxegol at the studied concentrations up to 16 µM caused no induction in the enzyme activity and mRNA levels for CYP1A1/2, CYP2B6 and CYP3A4/5 for all three donors tested.

Table 29: In vitro assessment of enzyme induction potential of naloxegol in human hepatocytes

NKTR-118 concentration (µM)	Mean induction CYP1A2 activity (fold increase)			Mean induction CYP1A2 mRNA expression (fold increase)		
	Donor 228	Donor 307	Donor 321	Donor 228	Donor 307	Donor 321
0.1	1.1	1.1	1.1	0.88	0.51	1.2
0.2	1.1	0.99	1.1	0.94	0.79	0.86
0.6	1.0	0.90	1.0	0.97	0.71	0.83
1.8	0.84	0.92	0.95	0.88	0.79	0.72
5.3	0.9	0.77	0.76	0.91	0.76	0.59
16	0.96	0.82	0.69	1.0	0.85	0.58

NKTR-118 concentration (μM)	Mean induction CYP2B6 activity (fold increase)			Mean induction CYP2B6 mRNA expression (fold increase)		
	Donor 228	Donor 307	Donor 321	Donor 228	Donor 307	Donor 321
0.1	1.2	1.3	1.3	0.96	1.0	0.79
0.2	1.4	1.4	1.4	0.97	1.3	0.75
0.6	1.2	1.2.	1.2	1.0	1.1	0.89
1.8	1.3	1.5	1.1	1.0	1.3	0.69
5.3	1.3	1.3	1.1	1.2	1.3	0.73
16	1.4	1.2	1.0	1.1	1.6	0.66
NKTR-118 concentration (μM)	Mean induction CYP3A4/5 activity (fold increase)			Mean induction CYP3A4/5 mRNA expression (fold increase)		
	Donor 228	Donor 307	Donor 321	Donor 228	Donor 307	Donor 321
0.1	0.93	1.0	1.0	1.0	0.6	1.3
0.2	0.93	0.9	0.93	1.0	0.91	1.0
0.6	0.82	0.82	0.92	1.1	0.96	0.73
1.8	0.78	0.84	0.79	1.1	1.2	1.0
5.3	0.52	0.55	0.45	1.3	1.5	0.56
16	0.32	0.40	0.19	1.5	2.0	0.56

Inhibition potential: *Naloxegol is an inhibitor of CYP2D6 with a mean IC50 of 84.7 μM in HLM. No inhibition of CYP1A, CYP2C9, and CYP2C19 was observed (IC50>100 μM). Based upon the in vivo concentrations noted for naloxegol, the IC50 values do not appear to be clinically relevant. The conclusions were based on the study described below:*

Study LS-2007-064 assessed the inhibition potential of CYP1A, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 by naloxegol in human liver microsomes (HLM). Seven concentrations (one replicate per concentration) of naloxegol (0, 0.2, 1, 2, 10, 20, and 100 μM) were incubated at 37 °C with HLM and NADPH (1 mM) in the presence of the probe substrates. The model substrates (concentration and incubation time) are: ethoxyresorufin (0.5 μM, 5 min) for CYPA1, tolbutamide (120 μM, 60 min) for CYP2C9, S-mephenytoin (25 μM, 60 min) for CYP2C19, and dextromethorphan (5 μM, 30 min) for CYP2D6. Midazolam (2.5 μM, 5 min) and testosterone (50 μM, 5 min) were used as probe substrates for CYP3A4. The following selective inhibitors with various concentrations were served as positive controls: α-naphthoflavone (0.006 to 3 μM) for CYP1A, sulphaphenazole (0.1 to 50 μM) for CYP2C9, ticlopidine (0.006 to 3 μM) for CYP2C19, quinidine (0.06 to 3 μM) for CYP2D6, and ketoconazole (0.006 to 3 μM) for CYP3A4. The results were shown in the table below.

Table 30: Enzyme inhibition potential of naloxegol in vitro in human liver microsomes

Cyp	CYP1A	CYP2C9	CYP2C19	CYP2D6	CYP3A4 (Midazolam)	CYP3A4 (Testosterone
IC_{50}	NC	NC	NC	84.7	NC	NC
Inhibn at 100 μM (%)	-	-	38.2	-	41.4	-

NC not calculated, >100 μM

Naloxegol is an inhibitor of CYP2D6 with a mean IC_{50} of 84.7 μM. No inhibition of CYP1A, CYP2C9, and CYP3A4 (testosterone as a CYP3A4-specific substrate) was observed up to a naloxegol concentration of 100 μM. While no IC_{50} values were obtained for CYP2C19 and CYP3A4 (midazolam as a CYP3A4-specific substrate), 38.2% and 41.4% inhibition were observed at 100 μM (65200 ng/mL) naloxegol, respectively. This may indicate the potential of naloxegol to act as an inhibitor of CYP2C19 and CYP3A4 at very high concentrations (much higher than the therapeutic concentrations). However, no clinical relevant effect is expected since the concentration causing inhibition was 1000 times more than clinically observed Cmax.

No time dependent inhibition (TDI) was observed for naloxegol in HLM at 50 μM for CYP1A2, CYP2C9, CYP2C19 andCYP2D6. No TDI was observed for naloxegeol at 10 μM (6520 ng/mL) for CYP3A4/5. However, TDI was observed at 50 μM (32600 ng/mL) for CYP3A4/5 with a mean %TDI value of 24.3%. It is unlikely that naloxegol produces TDI in in vivo at the clinical relevant Cmax. The conclusions were based on the study described below:

Study ADME-AZS-Wave3-130226 assessed the potential of naloxegol as a time dependent inhibitor of human CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 in pooled human liver microsomes (HLM). Naloxegol at 10 and 50 µM in the presence of NADPH (100 mM) was incubated with HLM for 30 minutes followed by 10 fold dilution and co-incubation with a CYP enzyme marker substrate cocktail for 15 minutes. The following marker substrates were present in a single cocktail: phenacetin (CYP1A2, 90 µM), diclofenac (CYP2C9, 30 µM), (S)-mephenytoin (CYP2C19, 105 µM), bufuralol (CYP2D6, 15 µM) and midazolam (CYP3A4/5, 9 µM) at 3 times their Km concentration. The following CYP isoform-selective time dependent inhibitors were used as positive controls: furafylline (CYP1A2, 10 µM), tienilic acid (CYP2C9, 2.5 µM), ticlopidine (CYP2C19, 5 µM), paroxetine (CYP2D6, 5 µM), and troleandomycin (CYP3A4/5, 1.5 µM). The results are shown in the table below.

Table 31: Evaluation of time-dependent inhibition potential by naloxegol for various CYPs

Naloxegol Concentration (µM)	Time dependent inhibition of substrate metabolism (%)				
	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4/5
10	<20	<20	<20	<20	<20
50	<20	<20	<20	<20	24.3

20% is defined as the cut off for determination of time dependent inhibition in this assay

No time dependent inhibition was observed for naloxegol at 10 µM for CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 and at 50 µM for CYP1A2, CYP2C9, CYP2C19 and CYP2D6. Time dependent inhibition was observed at 50 µM for CYP3A4/5 with a mean %TDI value of 24.3% indicating that naloxegol produces time dependent inhibition of CYP3A4/5 in HLM at a concentration of 50 µM (32600 ng/mL).

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Naloxegol as a P-gp substrate: Naloxegol is a human P-gp substrate in the in vitro system (Caco-2 cells).

Study RD00001771 investigated whether naloxegol (10 µM) is a substrate of human P-gp in the Caco-2 cells using native expression of P-gp and inhibition with cyclosporine A (10 µM), verapamil (100 µM), and elacridar (0.5 µM). Propranolol was used as a higher permeability marker and atenolol was used as a low permeability markers. Naloxone (10 µM) was also included in the study for comparison.
The results of the bidirectional permeability studies in Caco-2 cells indicated that naloxegol, but not naloxone is a substrate for P-gp (see Table #). Naloxegol has an efflux ratio of 15 that is sensitive to 3 different inhibitors of the P-gp, cyclopsporin, verapamil and elacridar. Naloxone in contrast, could be classified as a non-substrate. In addition, the passive permeability of naloxegol, measured in the presence of inhibitors of efflux transporters is significantly lower than that of naloxone, suggesting that PEG conjugation reduces the passive permeability of naloxegol. A reduced passive permeability coupled with an interaction with efflux transporters could potentially limit the oral absorption of naloxegol.

Table 32: Apparent permeability of naloxegol (NKTR-118) and naloxone with and without inhibitors.

	P_{app} A-B (10^{-6} cm/s)	P_{app} B-A (10^{-6} cm/s)	Efflux Ratio
Naloxone	27.3	25.0	0.91
NKTR-118	0.7	8.4	15.4
NKTR-118 + CsA	1.8	1.8	1.0
NKTR-118 + verapamil	1.3	1.7	1.3
NKTR-118 + elacridar	2.3	2.5	1.1

Naloxegol as an inhibitor of human transporters: Naloxegol (3 to 100 µM) is not an inhibitor of P-gp, OCT2, OAT1, OAT3, OATP1B1, OATP1B3, and BCRP mediated transport in the in vitro system.

Study OPT-2010-114 assessed whether naloxegol (3, 10, and 30 µM) is an inhibitor of human P-gp, BCRP, OAT1, OAT3, OCT2, OATP1B1, or OATP1B3 in the in vitro system. For transporters represented by the solute carrier (SLC) family, the uptake system was comprised of a polarized monolayer of MCDK-II cells. The probe substrates

used for OCT2, OAT1, OAT3, OATP1B1 and OATP1B3 were metformin (10 μM), p-aminohippurate (2 μM), estrone-3-sulfate (750 nM), estradiol-17β-d-glucuronide (2 μM), and bromosulfophthalein (2 μM), respectively. For P-gp, the system was comprised of a polarized monolayer of MDCK-II cells. The probe substrate was digoxin (100 nM). For BCRP, the system was comprised of a polarized cell monolayer of Caco-2 cells. The probe substrate was genistein (25 nM).
Each positive inhibitor met its acceptance criteria. Naloxegol (3 to 100 μM) is not an inhibitor of OCT2, OAT1, OAT3, OATP1B1, OATP1B3, P-gp, and BCRP mediated transport. IC50 values are greater than 100 μM for all of the transporters evaluated.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Naloxegol is a substrate for P-gp but does not appear to be the substrate of human OATP1B1, OATP1B3, or BCRP. Naloxegol is not an inhibitor of OCT2, OAT1, OAT3, OATP1B1, OATP1B3, P-gp, and BCRP. The conclusions were based on the studies described below:

Assessment on naloxegol as a substrate for human transporters, OATP1B1, OATP1B3, and BCRP
Study OPT-2010-113 assessed whether naloxegol (3, 10, and 30 μM) is a substrate of human OATP1B1, OATP1B3, or BCRP in MDCK and Caco-2 cells. For OATP1B1 and OATP1B3 transporters, transfected MDCK cells were used. The probe substrates used for OATP1B1 and OATP1B3 were estradiol-17β-d-glucuronide (2 μM) and bromosulfophthalein (2 μM), respectively. For BCRP, the system was comprised of a polarized monolayer of Caco-2 cells. The probe substrate was genistein (25 nM).
The results are shown in the table below. Each probe substrate transport amount met its acceptance criteria.

Table 33: Evaluation of substrate potential of naloxegol for various transporters

OATP1B1 and OATP1B3

Substrate	OATP1B1 Net uptake (pmol/min/cm^2)	OATP1B3 Net uptake (pmol/min/cm^2)
Naloxegol 3μM	0.000637 ± 0.000168	0.000637 ± 0.000287
Naloxegol 10μM	0.000147 ± 0.00146	0.000894 ± 0.000795
Naloxegol 30 μM	0.00293 ± 0.000851	0.00293 ± 0.000965
Estradiol-17 β-d-glucuronide 2μM	0.887 ± 0.126	-
Bromosufophthalein 2μM	-	2.08 ± 0.491

BCRP

Substrate	Papp (nm/sec) B to A	Papp (nm/sec) A to B	Efflux ratio
Naloxegol 3μM	0.164 ± 0.00375	0.00121 ± 0.00401	13.6
Naloxegol 3μM + chrysin	0.144 ± 0.0114	0.029 ± 0.00294	4.99
Naloxegol 10μM	0.169 ± 0.00713	0.0116 ± 0.00221	14.5
Naloxegol 10μM + chrysin	0.171 ± 0.00265	0.0365 ± 0.0143	4.68
Naloxegol 30μM	0.2 ± 0.010	0.0 ± 0.010	9.12
Naloxegol 30μM + chrysin	0.1 ± 0.003	0.0 ± 0.024	3.49
Genistein 25nM	458 ± 3.130	78.6 ± 6.79	5.82
Genistein 25nM + chrysin	260 ± 4.120	254.0 ± 12.6	1.02

Overall, naloxegol does not appear to be a substrate for human OATP1B1, OATP1B3, or BCRP. For OATP1B1, at 3 and 10 μM, the net amount of [^{14}C]-naloxegol transported in cells expressing OATP1B1 was not statistically different from the control cells. Although at 30 μM the net transport amount in the cells expressing OATP1B1 was statistically different from corresponding control cells ($p<0.05$), the overall net transport amount was only 0.3% of what was observed for probe substrate estradiol-17β-d-glucuronide.
For OATP1B3, while at 3 and 30 μM the net amount of [^{14}C]-naloxegol transported in cells expressing OATP1B3 were statistically different from corresponding control cells ($p<0.05$), the overall net transport amount was only 0.03% and 0.14 %, respectively, of what was observed for probe substrate bromosulfophthalein. At 10 μM, the net transport amount in cells expressing OATP1B3 was not statistically different from corresponding control cells.
For BCRP, the efflux ratios at 3, 10, and 30 μM of [^{14}C]-naloxegol transport was 13.6, 14.5, and 9.12, respectively. The efflux ratios were reduced to 4.99, 4.68, and 3.49, respectively, in the presence of 100 μM chrysin. However, this reduction was largely due to the modest change in the A→B flux of [^{14}C]-naloxegol. The net B→A flux of [^{14}C]- naloxegol in Caco-2 cells was reduced by about 20% in the presence of 100 μM chrysin, a concentration expected to abolish BCRP transport. Therefore, the efflux of [^{14}C]-naloxegol does not appear to be substantially mediated by BCRP.

Naloxegol as a P-gp substrate
Naloxegol is a human P-gp substrate in Caco-2 cells. The conclusions were based on the study described below:

Study RD00001771 investigated whether naloxegol (10 µM) is a substrate of human P-gp in the Caco-2 cells using native expression of P-gp and inhibition with cyclosporine A (10 µM), verapamil (100 µM), and elacridar (0.5 µM). Propranolol was used as a higher permeability marker and atenolol was used as a low permeability marker. The results of the bidirectional permeability studies in Caco-2 cells indicated that naloxegol, but not naloxone is a substrate for P-gp. Naloxegol has an efflux ratio of 15 that is sensitive to 3 different inhibitors of the P-gp, cyclopsporin, verapamil and elacridar. In addition, the passive permeability of naloxegol, measured in the presence of inhibitors of efflux transporters is significantly lower than that of naloxone, suggesting that PEG conjugation reduces the passive permeability of naloxegol. A reduced passive permeability coupled with an interaction with efflux transporters could potentially limit the oral absorption of naloxegol.

Table 34: Apparent permeability of naloxegol (NKTR-118) and naloxone with and without inhibitors.

	P_{app} A-B (10^{-6} cm/s)	P_{app} B-A (10^{-6} cm/s)	Efflux Ratio
Naloxone	27.3	25.0	0.91
NKTR-118	0.7	8.4	15.4
NKTR-118 + CsA	1.8	1.8	1.0
NKTR-118 + verapamil	1.3	1.7	1.3
NKTR-118 + elacridar	2.3	2.5	1.1

Naloxegol as an inhibitor of human transporters

Naloxegol (3 to 100 µM) is not an inhibitor of OCT2, OAT1, OAT3, OATP1B1, OATP1B3, P-gp, and BCRP mediated transport in MDCK and Caco-2 cells. The conclusions were based on the study described below:

Study **OPT-2010-114** assessed whether naloxegol (3, 10, and 30 µM) is an inhibitor of human P-gp, BCRP, OAT1, OAT3, OCT2, OATP1B1, or OATP1B3 in MDCK and Caco-2 cells. For transporters represented by the solute carrier (SLC) family, the uptake system was comprised of a polarized monolayer of MDCK-II cells. The probe substrates used for OCT2, OAT1, OAT3, OATP1B1 and OATP1B3 were metformin (10 µM), p-aminohippurate (2 µM), estrone-3-sulfate (750 nM), estradiol-17β-d-glucuronide (2 µM), and bromosulfophthalein (2 µM), respectively. For P-gp, the system was comprised of a polarized monolayer of MDCK-II cells. The probe substrate was digoxin (100 nM). For BCRP, the system was comprised of a monolayer of Caco-2 cells. The probe substrate was genistein (25 nM).

Naloxegol (3 to 100 µM) is not an inhibitor of OCT2, OAT1, OAT3, OATP1B1, OATP1B3, P-gp, and BCRP mediated transport. IC_{50} values are greater than 100 µM for all of the transporters evaluated.

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Naloxegol is co-administered with opioid drugs as the proposed indication is the treatment of opioid-induced constipation. Naloxegol did not alter pharmacokinetics of morphine in a PK study in volunteers.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Opioid analgesics will be co-administered with naloxegol due to the proposed indication.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Yes, in vivo DDI studies with potent or moderate CYP3A4/P-gp inhibitors or inducers and with P-gp inhibitor quinidine demonstrated significant changes in naloxegol exposure. Please refer to response to question 2.4.1 in this section.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

The proposed mechanism of action for this peripherally acting opioid receptor antagonist drug, suggests that when administered concomitantly with opioid drugs in chronic non-cancer patients, naloxegol will act via the peripheral

mu-opioid receptors to reverse the constipation induced by opioid analgesics through these very receptors. On the other hand, central effects of opioid drugs (e.g. analgesia) mediated via the mu-opioid receptors may also be antagonized, if the drug crosses the blood-brain barrier. Sponsor claims that the pegylation renders the molecule to be a substrate of P-gp and thereby reduces its BBB permeability. Exploratory pharmacodynamics evaluation in volunteers indicated no effect of various naloxegol single doses up to 1000 mg on morphine-induced pupillary constriction, a central effect. However, the value of this endpoint is questionable. Please refer to the clinical review with regard to evidence of loss of analgesia or evidence of withdrawal symptoms in chronic non-cancer pain patients while on naloxegol.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

The metabolism, metabolic profiling, protein binding and drug-interaction potential of naloxegol has been adequately addressed through various in vitro and in vivo studies.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

There are no significant omissions with regard to Clinical Pharmacology content. The proposed dose of 25 mg *qd* for the general patient population appears acceptable; however a dose reduction to 12.5 mg *qd* may be considered for patients who are unable to tolerate the higher dose, (b) (4) In phase 3 trials, the dose-response for the 12.5 mg and 25 mg naloxegol doses in terms of efficacy outcomes was at best shallow.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

The Applicant reports that naloxegol oxalate is a BCS Class 3 compound. Refer to Dr. Kareen Riviere's biopharmaceutics review for the evaluation of data supporting this classification.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

Information from the pivotal BE study (reviewed by Dr. Kareen Riviere) suggests ~ 94 % relative bioavailability for the phase 3 naloxegol formulation relative to the proposed commercial oxalate formulation.

2.5.2.1.1 What data support or do not support a waiver of in vivo BE data?

The Applicant provided comparative dissolution data in pH 1.2, pH 4.5, and pH 6.8 to support granting the biowaiver for the 12.5 mg strength. These data are acceptable per Dr. Kareen Riviere. Refer to her biopharmaceutics review for the evaluation of data supporting the biowaiver.

2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

Per Dr. Kareen Riviere, the BE study to bridge Phase 3 and commercial formulations met the 90% CI using equivalence limits of 80-125%. Refer to her biopharmaceutics review for the evaluation of the BE data.

2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Not applicable

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Two separate studies evaluated the food-effect on PK for the clinical trial (naloxegol) and commercial (naloxegol oxalate) formulations. Plasma concentrations of naloxegol were greater under fed conditions for both the phase III (Cmax and AUC higher by 47 % and 55 %, respectively) and commercial (Cmax and AUC higher by 30 % and 46 %, respectively) formulations. In the clinical trials for naloxegol, dose was administered under fasted conditions (approximately 1 h before food in the morning). Proposed labeling recommends that drug should be dosed on an empty stomach. Dosing in the morning is recommended for patient convenience to preferably avoid bowel movements during the night. This appears reasonable.

An overview of the results from the two food-effect PK studies is provided below:

Study D3820C00025: This study compared two different oxalate formulations against the reference phase III naloxegol formulation in fed and fasted conditions. Study was an open-label, randomized, cross-over, single-dose, 2-part study. In part B, the food-effect on PK was evaluated for one of the oxalate variants (formulation 1) and the phase III formulation.

Mean plasma naloxegol concentration-time data are shown for reference phase III formulation 3 under fed and fasted conditions:

Linear Scale **Formulation 3 (fasted vs. fed)**

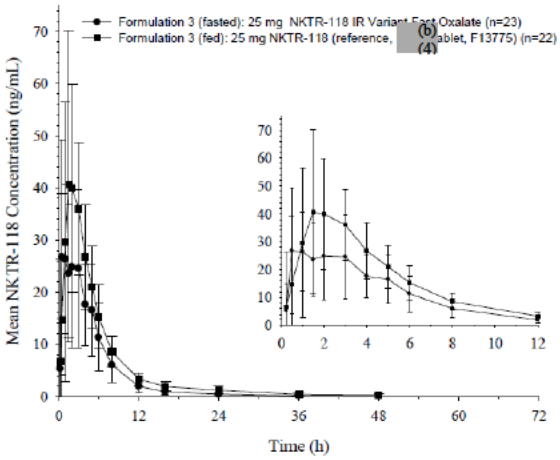


Figure 25: Plasma naloxegol concentration-time profiles for the proposed naloxegol oxalate formulation under fed and fasted conditions.

Plasma concentrations of naloxegol from the phase III formulation were greater under fed conditions. Statistical comparison of the relative bioavailability information is shown below for formulation 3 (Form 3 i.e. reference or phase III naloxegol formulation):

Table 35: Statistical analyses of food-effect information for two different oxalate formulations against the free base

							Comparisons	
Param	**Tmt[a]**	**State**	**n**	**Geo LS mean**	**95% CI**	**Pair**	**Ratio (%)**	**90% CI**
AUC (ng·h/mL)	Form 1	Fasted	22	161.0	(138.7, 187.0)			
		Fed	20	228.1	(195.4, 266.4)	Fed/Fasted	141.69	(129.27, 155.31)
	Form 3	Fasted	23	150.5	(127.6, 177.5)			
		Fed	21	234.0	(197.5, 277.2)	Fed/Fasted	155.47	(137.84, 175.36)
C_{max} (ng/mL)	Form 1	Fasted	22	33.26	(28.25, 39.16)			
		Fed	20	44.79	(37.68, 53.24)	Fed/Fasted	134.65	(113.81, 159.30)
	Form 3	Fasted	23	33.38	(27.16, 41.03)			
		Fed	22	48.96	(39.72, 60.35)	Fed/Fasted	146.66	(124.76, 172.42)

Study D3820C00018: Study included an assessment of the food-effect on PK for the commercial (naloxegol oxalate) formulation. The assessment was part of a 3-way crossover study in 42 healthy male and female volunteers. Mean plasma-concentrations of naloxegol commercial formulation under fasted (A) and fed (B) conditions are shown in the figure below [compare A (fasted) vs. B (fed) to evaluate food-effect on PK for the proposed formulation]:

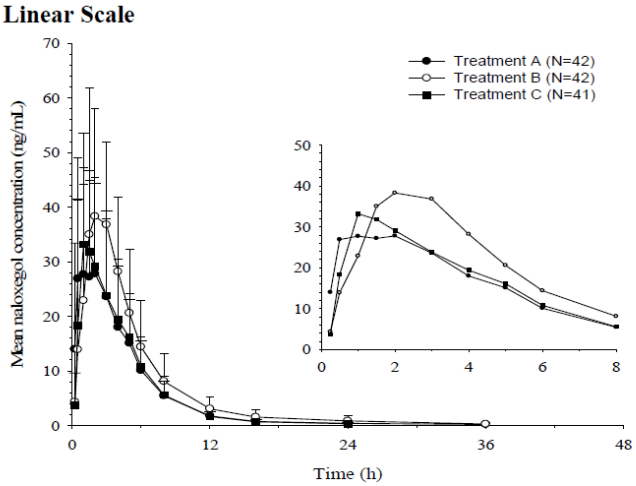


Figure 26: Plasma naloxegol concentration-time profiles for clinical vs. proposed formulations; includes food-effect data (Treatment A vs Treatment B) for the commercial oxalate formulation;

At a glance, concomitant dosing with food appears to have increase the peak and overall naloxegol plasma concentrations and prolonged the Tmax relative to dosing under fasted conditions. Statistical comparisons of food-effect (Treatments A vs. B):

Table 36: Statistical analyses of the food-effect information for the proposed commercial formulation

						Comparisons		
Parameters	**Tmt[a]**	**State**	**n**	**Geo LS mean**	**95% CI (%)**	**Pair**	**Ratio (%)**	**90% CI (%)**
AUC (ng·h/mL)	A	Fasted	42	144.6	(126.56, 165.33)	B/A	145.09	(137.09, 153.56)
	B	Fed	42	209.9	(183.62, 239.87)			
$AUC_{(0-t)}$ (ng·h/mL)	A	Fasted	42	142.4	(124.48, 162.80)	B/A	145.72	(137.56, 154.35)
	B	Fed	42	207.4	(181.39, 237.22)			
$AUC_{(0-24)}$ (ng·h/mL)	A	Fasted	42	140.5	(123.16, 160.20)	B/A	143.60	(135.58, 152.10)
	B	Fed	42	201.7	(176.86, 230.05)			
C_{max} (ng/mL)	A	Fasted	42	38.35	(33.13, 44.39)	B/A	129.51	(115.66, 145.02)
	B	Fed	42	49.66	(42.90, 57.49)			

2.5.4 When would a fed BE study be appropriate and was one conducted?

Since dosing in clinical trials was under fasted conditions, and the proposed labeling calls for dosing under fasted conditions, a fed bioequivalence study is not necessary. However, food effect on PK for the clinical and to-be-marketed formulations has been evaluated.

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

Please refer to Dr. Kareen Riviere's Biopharmaceutics review of this NDA.

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Not applicable

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable

2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

There are no unaddressed relative bioavailability or bioequivalence issues from a Clinical Pharmacology perspective.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Active moieties were identified and measured in plasma and urine using validated HPLC-MS/MS or LC APIMS/MS detection methods.

2.6.2 Which metabolites have been selected for analysis and why?

Metabolite profiling studies from phase 1 studies including mass balance study, dose escalation PK study, as well from the phase 2b study in OIC patients identified several metabolites, none of which had an abundance that was > 10 % that of parent naloxegol i.e.. no major metabolite has been identified for naloxegol. Hence metabolites were not specifically assessed in subsequent Clinical Pharmacology studies. In addition, the presence of naloxegol-glucuronide was evaluated in early phase I and in phase 2b studies using a validated analytical method. Glucuronide levels were below detection at the clinically relevant dose of 25 mg *qd*. Naloxone levels were assessed in phase 1 and phase 2b studies to determine whether complete removal of PEG side chain occurs during metabolism leading to the formation of this central opioid antagonist. Naloxone was not found during in vitro incubations or in the in vivo studies using the assay used for this purpose with an LOQ of 0.25 ng/mL. The LOQ employed appeared much higher than those found in publications and therefore lack of naloxone in these studies can rule out levels above 0.25 ng/mL but not below this level. The clinical relevance of such levels in terms of central antagonism is not known.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Measurement of analytes in plasma yields total concentrations. This is acceptable as the plasma protein binding of naloxegol is very low (~ 4 %) and most of the drug in circulation is unbound.

2.6.4 What bioanalytical methods are used to assess concentrations?

Across the Clinical Pharmacology studies, naloxegol (7-PEG-Naloxol or NKTR-118) alone was identified in plasma or urine using validated HPLC with MS/MS detection (method NKTHPP; (b) (4)), or by simultaneous detection of naloxegol, naloxone and naloxegol- glucuronide by LC- API MS/MS method (b) (4). Subsequently, a partial validation of above simultaneous detection method by (b) (4) was conducted for analysis of naloxegol alone in plasma.

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

Method NKTHPP for Plasma: The HPLC method with MS/MS detection for the determination of naloxegol in human plasma was validated sufficiently over 0.1 to 50 ng/mL concentration range. The calibration model was assessed to be linear regression with 1/X2 weighting.

Method NKTHPP for urine: This method has been successfully validated for the determination of naloxegol in human urine (treated with Triton X-100). The method was validated in the range of 25.0 to 5000 ng/mL. The mean r2 value for calibration curves was 0.9995.

Method ARNAL2: The LC-API/MS/MS (liquid chromatography atmospheric pressure ionization tandem mass spectrometry) method was validated in human plasma for detection of naloxone, 7-PEG-naloxol, and naloxegol-Glucuronide (7PN-Gluc). Naltrexone was used as the internal standard. The calibration curves were acceptable over a range of 0.250 – 125 ng/mL for Naloxone, 0.100 – 50.0 ng/mL for 7-PEG-Naloxol, and 0.500 – 250 ng/mL for 7PN-Gluc.

Method ARNAL3: A partial validation of the above method was conducted to evaluate naloxegol alone in human plasma over a calibration range of 0.1 – 50 ng/mL.

The range of standard curves is deemed sufficient for sample analyses in Clinical Pharmacology studies based on the observed concentrations; the methods also demonstrated a dilution integrity up to 50-fold which allows samples above the calibration range to be diluted for analysis.

The r2 values for calibration curves were ≥ 0.98. No significant matrix interference was noted in the assay in any sample at or near the retention time of the analyte or the internal standard. No significant injector carryover was noted for either analyte or internal standard.
2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

For the HPLC with MS/MS detection, for the detection of naloxegol in plasma samples, the LLOQ was set at 0.1 ng/mL and the ULOQ was 50 ng/mL.

For the HPLC with MS/MS detection, for detection of naloxegol in urine samples the LLOQ set at 25.0 ng/mL and ULOQ was set to 5000 ng/mL.

For the LC-API MS/MS method for simultaneous detection of analytes, the lower limit of quantitation (LLOQ) for Naloxone, 7-PEG-Naloxol, and 7PN-Gluc was 0.250, 0.100, and 0.500 ng/mL, respectively, using a 100 µL plasma aliquot.

For the partial validation of the LC-API MS/MS method to evaluate naloxegol alone in plasma, the LLOQ and ULOQ were set at 0.1 ng/ML and 50 ng/mL, respectively.

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

Method NKTHPP for plasma analysis of naloxegol using HPLC with MS/MS detection:
Using QC samples (0.1, 0.3, 5.0, and 40 ng/mL), the within-batch (for each batch) and the between batch precision, reported as coefficient of variation (%CV) and the within-batch and between-batch accuracy, reported as bias were found to be within acceptable ranges as shown:

Table 37: Validation parameters for the plasma HPLC-MS/MS assay of naloxegol

Batch	LLOQ	QC L	QC M	QC H	DilQC
	0.100	0.300	5.00	40.0	250
	ng/mL	ng/mL	ng/mL	ng/mL	ng/mL

Within-batch mean (ng/mL)	0.0901	0.273	4.84	38.7	NA
Within-batch CV (%)	6.4	3.3	1.8	3.5	NA
Within-batch Bias (%)	-9.9	-9.0	-3.2	-3.2	NA
n	6	6	6	6	NA
Within-batch mean (ng/mL)	0.101	0.291	5.00	39.3	235
Within-batch CV (%)	2.6	2.1	2.1	2.8	3.1
Within-batch Bias (%)	1.0	-3.0	0.0	-1.8	-6.0
n	6	6	6	6	6
Within-batch mean (ng/mL)	0.105	0.295	4.99	39.6	251
Within-batch CV (%)	7.7	2.9	1.4	2.5	13.0
Within-batch Bias (%)	5.0	-1.7	-0.2	-1.0	0.4
n	6	6	6	6	6
Between-batch mean (ng/mL)	0.0986	0.286	4.94	39.2	243
Between-batch CV (%)	8.6	4.3	2.3	2.9	9.9
Between-batch Bias (%)	-1.4	-4.7	-1.2	-2.0	-2.8
n	18	18	18	18	12

Method NKTHPP for urine naloxegol analysis using HPLC with MS/MS detection: Using QC samples of 25, 75, 500 and 4000 ng/mL, the within-batch (for each batch) and the between-batch precision, reported as coefficient of variation (CV), were found to be acceptable [≤15.0% at all levels (except ≤20.0% at LLOQ)]. The within-batch and between-batch accuracy, reported as bias, were within ±15.0% of the nominal concentration at all levels (except ±20.0% at LLOQ). In addition, the bias of one-half of the QC samples at each concentration and two-thirds of all QC samples were within ±15.0% (except ±20.0% at LLOQ) of the theoretical concentration. Acceptable accuracy and precision for determination of NKTR_118 were demonstrated in human urine.

Method ARNAL2 for simultaneous detection using LC-API MS/MS method: QCs used were as follows: For naloxone: 0.75, 20, 100 ng/mL; for 7-PEG-Naloxol: 0.3, 8, 40 ng/mL; for 7-PN-Gluc: 1.5, 40, 200 ng/mL. QC samples at the three concentrations in plasma were analyzed for intra- and inter-assay accuracy (bias) and precision (% CV) of the assay and to assess analyte stability. Accuracy values were within 85 -115 % of nominal concentrations for all analytes. Precision values were ≤ 15 % for all three analytes. Precision at the LLOQ was ≤ 20 % for all analytes.

Method ARNAL3 for partial validation of naloxegol detection in plasma: Three QCs prepared in control plasma (0.300, 8.00, and 40.0 ng/mL) showed acceptable intra- and inter-batch accuracy (within 85 -115 %) and precision (≤ 15 %). Accuracy and precision at LLOQ were 80-120 % and ≤ 20 %, respectively.

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, auto-sampler)?

HPLC with MS/MS detection:

Short-term stability in human plasma:	At least 76 hours at 2-8°C
Long-term stability in human plasma:	At least 386 days at -10 to -30°C
Freeze-thaw stability in human plasma:	6 cycles at -10 to -30°C
Stability in human whole blood:	At least 2 h at RT and on wet ice
Processed Samples Integrity:	15 days at 2 to 8°C and 1 day at RT

LC-API MS/MS method:

Stability of all analytes was established for three freeze/thaw cycles and at room temperature for 21 hours. All analytes were stable in plasma extracts for 53 hours at room temperature. Naloxone and 7-PEGNaloxol, but not 7PN-Gluc, were stable in extracts stored for 73 hours in the refrigerator (4°C). Naloxone in processed extracts was also stable at room temperature in the autoinjector for at least 61 hours and 7PN for at least 79 hours. This was quantified against both original and reinjected calibration curves. The autoinjector stability of 7PN-GLuc was also shown for 61 hours but only with the reinjected calibration curve. All analytes were stable when plasma samples were stored frozen at -20°C and -70°C for at least 34 days.

3 Detailed Labeling Recommendations

Labeling revisions are ongoing. Please refer to the final approved labeling when available. Detailed recommendations will be sent to the sponsor regarding the correct formatting and organization as well as the content related to Highlights, Dosage and Administration, Drug Interactions, Specific Populations as well as Clinical Pharmacology sections of the PLR labeling. The following dosing proposals or labeling language which are different from sponsor's original proposals, are being recommended by OCP:

- (b) (4)
- (b) (4)
- (b) (4)

4 Appendices

4.1 Consult Reviews

4.1.1. Pharmacometrics Review

4.1.2. PBPK Review

4.2 Cover Sheet and OCP Filing Memo

4.3 Individual Study Reviews

Please refer to Part 2 of the Clinical Pharmacology review in DARRTs for individual study reviews.

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

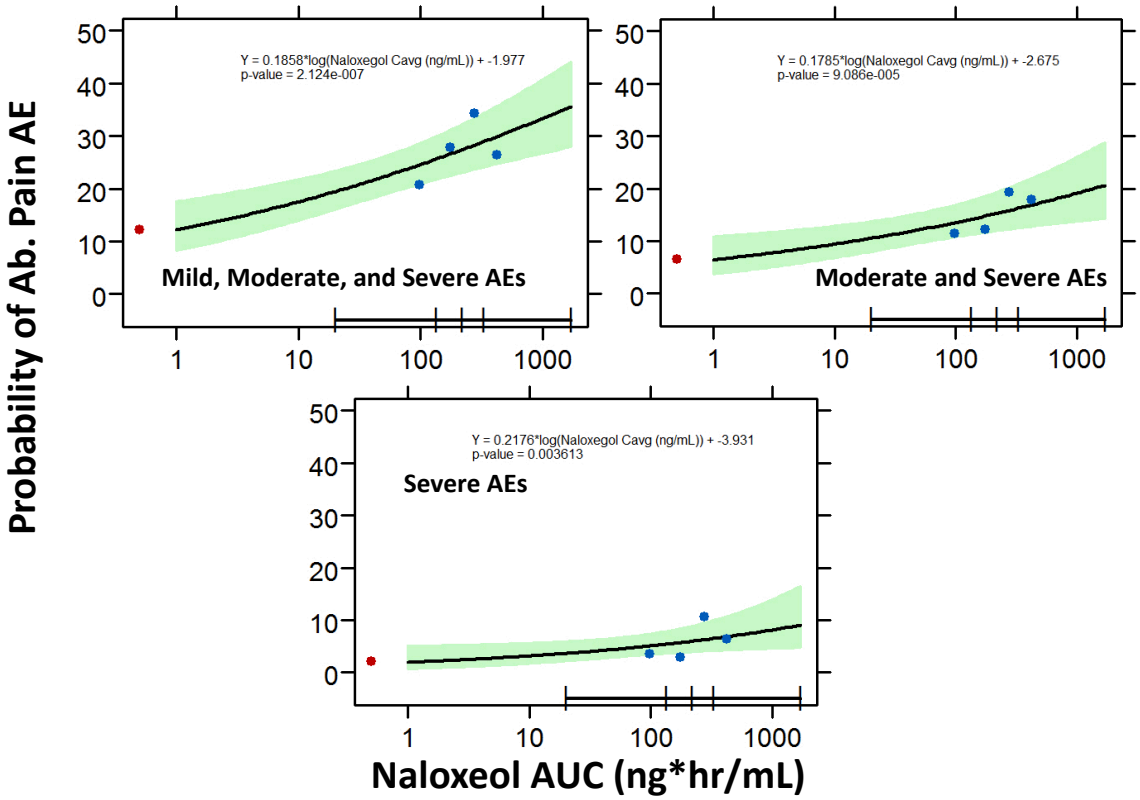
The purpose of this review is to address the following key question.

1.1.1 Should patients who cannot tolerate the 25 mg dose due to abdominal pain receive 12.5 mg naloxegol?

Yes, for patients that cannot tolerate the drug due to abdominal pain, it is recommended to reduce the dose to 12.5 mg prior to discontinuing the drug.

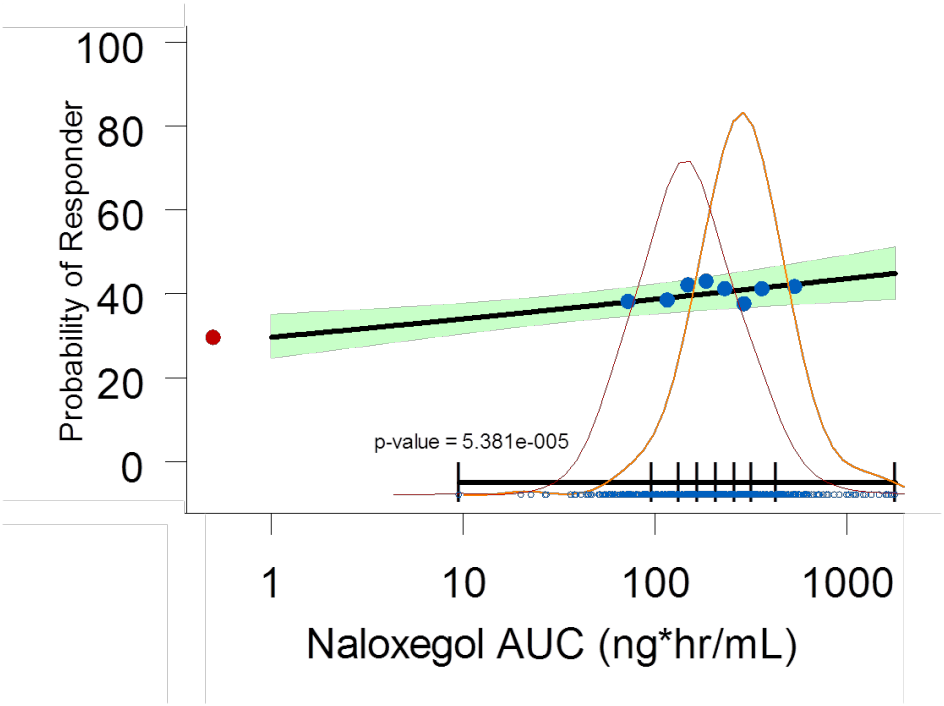
In Trials 04 and 05 there was a clear exposure-response relationship for abdominal pain (Figure 1). This relationship led to the question whether there may be benefit from giving patients who cannot tolerate the 25 mg dose 12.5 mg naloxegol.

Figure 1. Exposure-response relationships exist for abdominal pain by severity. The logistic regression and prediction interval is shown by the solid line and shaded region. The analysis was conducted on placebo and naloxegol data simultaneously, assuming placebo concentrations of naloxegol were zero. Data points are the probability for the placebo (red) and naloxegol (blue) exposure bins, denoted by the bars at the bottom of the plot.



In Trial 04, the 12.5 mg naloxegol dose was superior to placebo, yet it was numerically lower than 25 mg naloxegol arm. In the replicate trial 05, the primary efficacy response rates for both 12.5 mg naloxegol and 25 mg naloxegol treatment groups were decreased compared to trial 04 for unexplained reasons. Regardless of this decrease in study 05, the 12.5 mg arm is numerically better than placebo and the difference in efficacy between the 25 and 12.5 mg arm is similar to that in trial 04. Additionally, there is a significant exposure-response relationship (Figure 2) which provides evidence of effectiveness and demonstrates that the response rates for these two doses are not that far apart. While 12.5 may have failed superiority in trial 05, there appears to be an evidence to suggest that patients receiving 12.5 would still benefit over those receiving placebo.

Figure 2. Logistic regression for the primary efficacy endpoint (SBM responder, intent-to-treat analysis set) suggests that those with higher exposures exhibited the best response. Scatter points represent the probability of response for each exposure bin or placebo (red scatter point). Solid line is the logistic regression and the shaded region is the prediction interval. Red and orange lines indicate the density function for naloxegol exposure in the 12.5 and 25 mg doses, respectively.

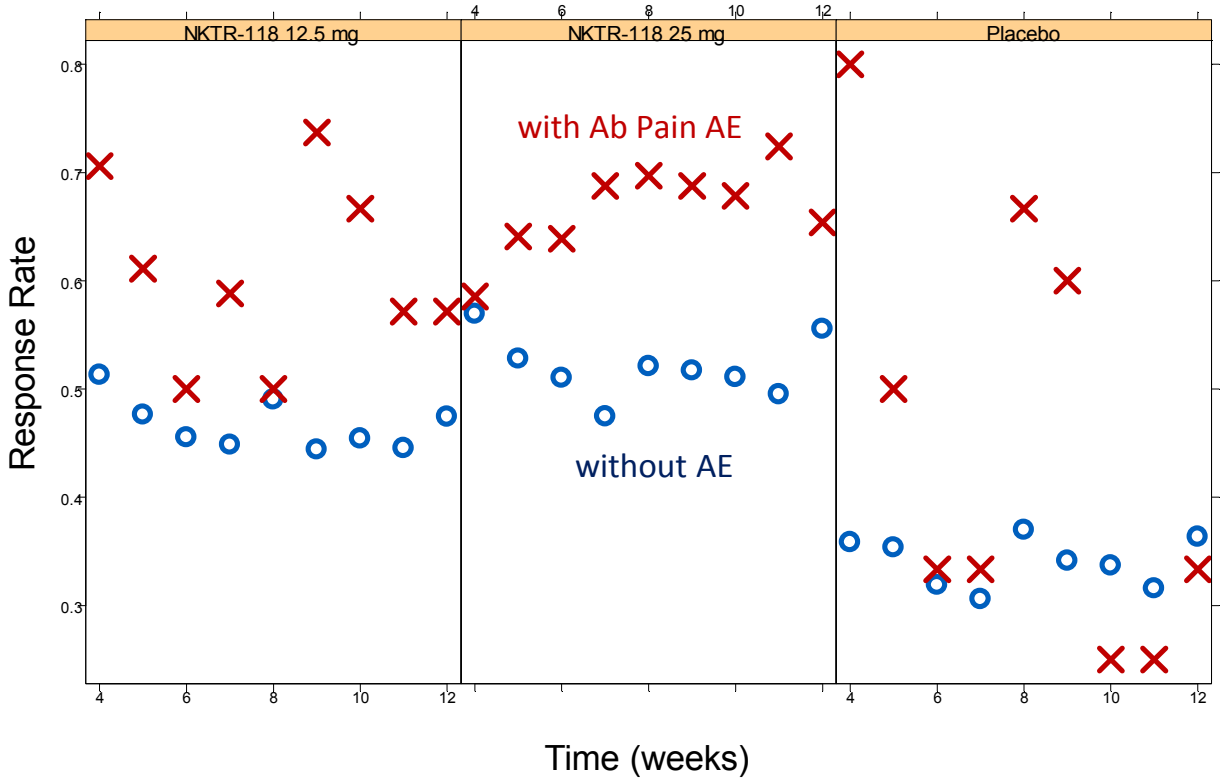


The 25 mg dose is the adequate starting dose for the overall population. For patients that cannot tolerate the drug due to abdominal pain, it is recommended to reduce the dose to 12.5 mg prior to discontinuing the drug. The following tables and figures show that, in general, patients with abdominal pain show greater response to naloxegol as assessed by both primary (Table 1, Figure 3) and secondary (Table, Figure) efficacy measures.

Table 1. Primary efficacy endpoint shows numerically higher response rate for those patients that experienced abdominal pain AEs compared to those who didn't.

	No Abdominal Pain AE		With Abdominal Pain AE	
Treatment	N	Response Rate (%)	N	Response Rate (%)
Placebo	131/449	29.1	11/32	34.4
NKTR-118 12.5 mg	158/422	37.5	25/56	44.4
NKTR-118 25 mg	163/392	41.6	45/100	44.8

Figure 3. Patients with abdominal pain adverse events appear to have higher response rates compared to those without abdominal pain AEs. Red X and blue circles represent the response rate* for patients with and without abdominal pain AEs, respectively. Data are from studies 04 and 05 combined.



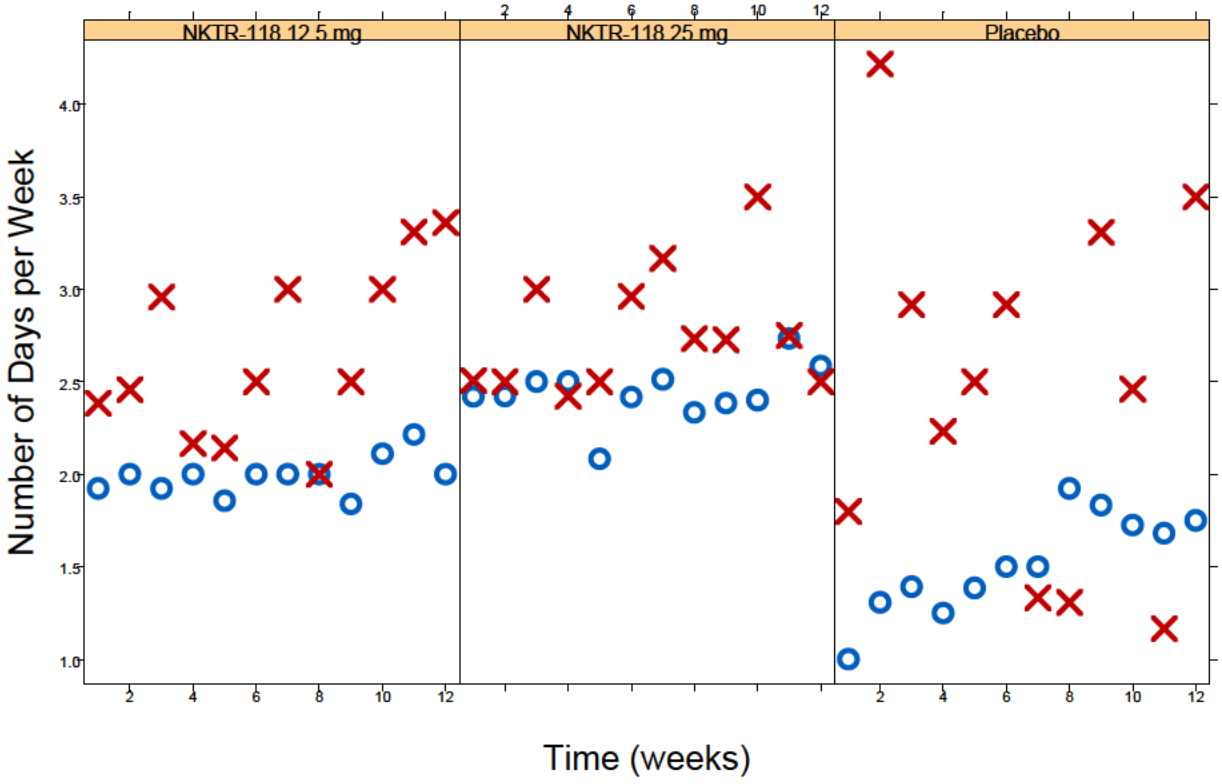
*Response rate was calculated for each week prior to week 12 to mimic the applicant's primary endpoint at week 12. At each week the patient must have had at least 3 SBMs and an increase of at least 1 from baseline. Additionally ¾ of all their prior weekly evaluations had to result in responder status and for 3 out of the last 4 weekly assessments the patient must have been responding.

The analysis was also performed for two secondary endpoints: 1) time to first post-dose SBM and 2) mean number of days per week where > 1 SBM.

Table 2. Patients with abdominal pain adverse events appeared to exhibit shorter durations to the first post dose SBM. Results are shown as the median for each treatment group for both studies 04 and 05.

	Time to first post-dose SBM (hr)	
Treatment	No Abdominal Pain AE	With Abdominal Pain AE
Placebo	37.5	23.1
NKTR-118 12.5 mg	15.1	3.4
NKTR-118 25 mg	20.8	3.3

Figure 3. The mean number of days per week where SBMs were greater than 1 appears to be higher for those patients with abdominal pain AEs compared to those without. Red X and blue circles represent the number of days per week where SBMs were > 1 for patients with and without abdominal pain AEs, respectively. Data are from studies 04 and 05 combined.



1.2 Recommendations

Division of Pharmacometrics has reviewed this NDA and has the following recommendations:

- As proposed by the applicant, 25 mg is an adequate starting dose for the overall population.
- Patients who cannot tolerate the 25 mg dose due to abdominal pain may consider dose reduction to 12.5 mg dose. (b) (4)

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

(b) (4)

2 PERTINENT REGULATORY BACKGROUND

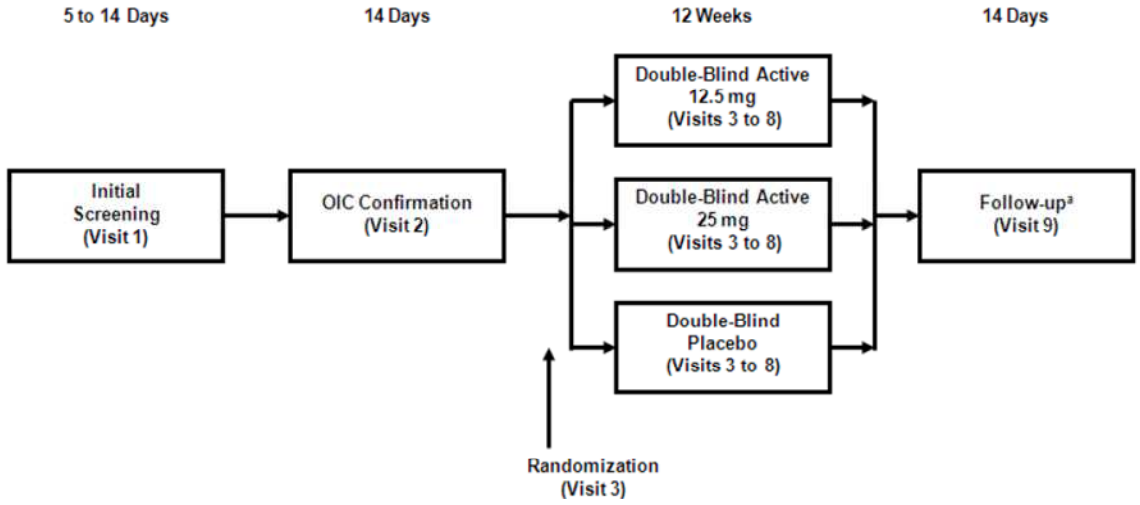
Naloxegol is a pegylated derivative of naloxone and a new molecular entity. The applicant is seeking use for the proposed indication of treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain. Please refer to section 3.1 below for the topline efficacy results from the registration trials.

3 RESULTS OF APPLICANT'S ANALYSIS

3.1 Clinical Trials:

Two replicate double-blind, randomized phase 3 studies were conducted to evaluate the safety and efficacy of naloxegol in patients with OIC, studies 04 and 05. The design of these trials is shown in Figure 4.

Figure 4. Schematic of Trial Designs for Studies 04 and 05



(Source: Applicant's Clinical Study Report, Figure 1)

Study 04: A total of 652 patients completed the OIC confirmation period, were randomized, and entered the double-blind treatment period. Of the randomized patients, 99.5% received treatment, 80.4% completed the study. (Source: Applicant's Clinical Study Report, Table 8)

Study 05: A total of 700 patients completed the OIC confirmation period, were randomized, and entered the double-blind treatment period. Of these patients, 697 (99.6%) received treatment, and 537 (76.7%) completed the study. (Source: Applicant's Clinical Study Report, Table 8)

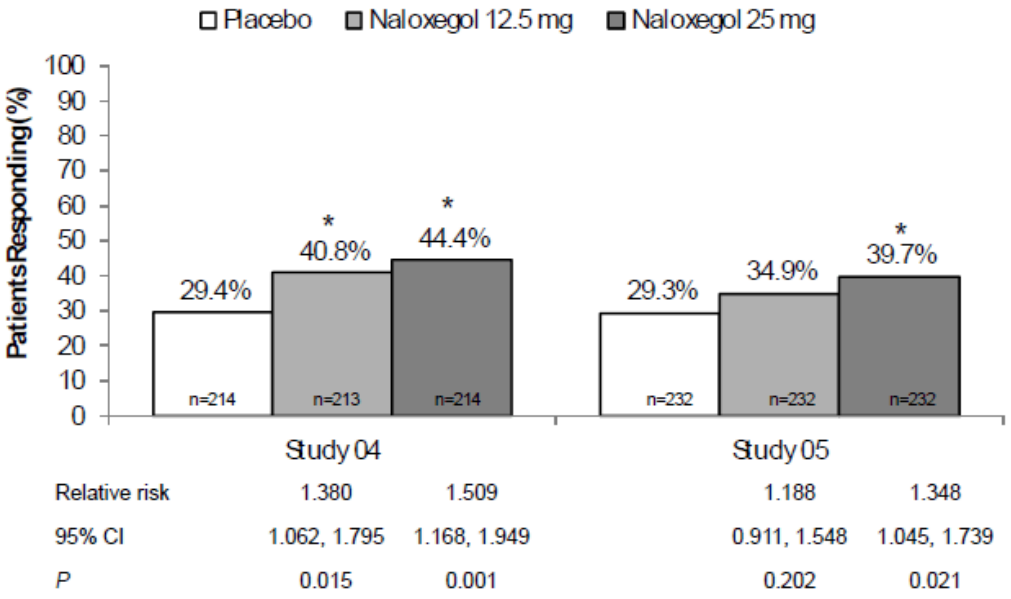
3.1.1 Efficacy Results for Trials 04 and 05:

Primary Endpoint:

The primary endpoint was defined as the responder rate at week 12. Patients were responding if they had at least 3 SBMs per week with a change from baseline of at least 1. In addition 9 out of the 12 weeks on treatment they had to be considered a responder and the last 3 out of 4 weeks on treatment they had to be considered a responder. To be a responder, patients were also required to meet a diary compliance criteria, where data was only accepted if the diary was completed for 4 days each week on treatment.

Figure 5 shows the results the applicant's replicate phase 3 efficacy trials for naloxegol. The 25 mg dose was statistically significant in both trials, whereas the 12.5 mg dose only showed statistical significance in trial 04. Regardless, there appears to be a clear numerical trend indicating better response for the 25 mg dose group.

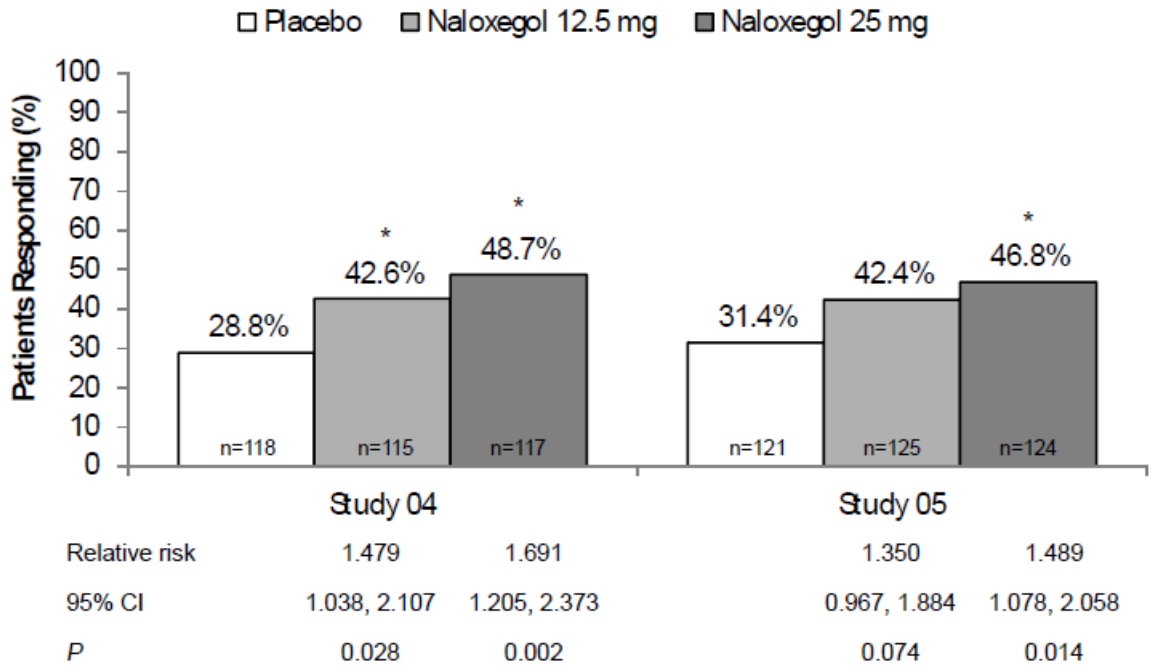
Figure 5. Applicant's Primary Efficacy Analysis



(Source: Summary of Clinical Efficacy, Figure 2)

Secondary Endpoints: The following three secondary endpoints were evaluated: 1) response in the LIR subgroup, 2) time to first post dose laxation, and 3) the mean number of days per week where the number of SBMs was at least one. These results for studies 04 and 05 are shown in (Figure 6, Table 4, and Table 5) and are consistent with the results of the primary endpoint.

Figure 6. Applicant's Efficacy Analysis in the LIR Subgroup



(Source, Clinical Summary of Efficacy, Figure 4)

Table 4. Applicant's analysis of time in hours to first post-dose SBM.

	Study 04			Study 05		
	Placebo (N = 214)	Naloxegol 12.5 mg (N = 213)	Naloxegol 25 mg (N = 214)	Placebo (N = 232)	Naloxegol 12.5 mg (N = 232)	Naloxegol 25 mg (N = 232)
Number of patients (%) with post-dose SBM	209 (97.7)	211 (99.1)	213 (99.5)	228 (98.3)	228 (98.3)	227 (97.8)
Median time (h) to first SBM [a] (95% CI)	35.8 (27.0,48.1)	20.4 (11.5,22.7)	5.9 (4.8,11.5)	37.2 (30.0,46.9)	19.3 (9.4,22.3)	12.0 (7.0,21.5)
SBM by ≤6 h (%)	33 (15.4)	72 (33.8)	109 (50.9)	40 (17.2)	80 (34.5)	91 (39.2)
SBM by ≤12 h (%)	49 (22.9)	93 (43.7)	122 (57.0)	57 (24.6)	102 (44.0)	115 (49.6)
SBM by ≤24 h (%)	79 (36.9)	125 (58.7)	150 (70.1)	85 (36.6)	136 (58.6)	142 (61.2)
HR (Comparison vs. placebo)[a]	NA	1.610	2.384	NA	1.590	1.576
95% CI	NA	1.320,1.963	1.933,2.940	NA	1.313,1.925	1.303,1.906
p-value	NA	<0.001*	<0.001*	NA	<0.001	<0.001*

[a] Estimates calculated using the Kaplan-Meier technique.
* Statistically significant under the MTP.
Note: The percentages are based on the number of intent-to-treat patients in each treatment group.
CI Confidence interval; SBM spontaneous bowel movement.

(Source, Clinical Summary of Efficacy, Table 12)

Table 5. Applicant's repeated measures analysis of the mean number of days per week with at least 1 SBM (and less than 4) over Weeks 1 to 12.

	Study 04			Study 05		
	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg
Baseline[a]						
n	213	213	214	232	232	232
Mean (SD)	1.3 (0.85)	1.4 (0.81)	1.2 (0.94)	1.4 (0.89)	1.5 (0.86)	1.3 (0.84)
Change from baseline						
LS mean (SE)	1.66 (0.13)	2.21 (0.13)	2.48 (0.13)	1.73 (0.12)	2.12 (0.12)	2.41 (0.13)
Difference vs Placebo[b]						
LS mean	NA	0.55	0.82	NA	0.39	0.68
95% CI	NA	0.24, 0.86	0.51, 1.13	NA	0.09, 0.69	0.37, 0.98
p-value	NA	<0.001	<0.001	NA	0.010	<0.001

[a] Baseline based on a patient's mean number of days with SBMs over the OIC confirmation period
[b] Analysis via MMRM with fixed effects for baseline, baseline laxative response, treatment and treatment time interaction. Study pooled center is included as a random effect.
* Statistically significant under the MTP.
Days with > 3 SBMs are /day are not included (Section 1.2.1.7)
CI Confidence interval; NA Not applicable; SBM Spontaneous bowel movement; SD Standard deviation; SE Standard error.

(Source, Clinical Summary of Efficacy, Table 13)

3.2 Population PK:

The applicant's population PK model was based on data from 14 studies shown in Table 6.

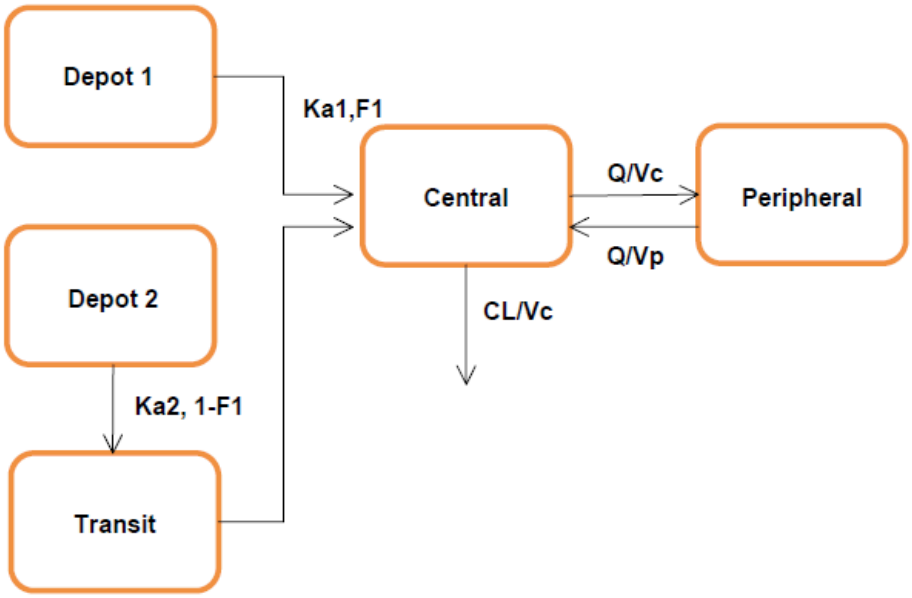
Table 6. Studies Incorporated in the Population PK Analysis.

Protocol Number	Short Title	Sampling Scheme	Number of Samples
05-IN-OX001	SAD Study	rich	569
07-IN-NX002	MAD Study	rich	839
08-PNL-04	Relative Bioavailability	rich	752
D3820C00009	Renal Impairment	rich	518
D3820C00010	Hepatic Impairment	rich	312
D3820C00014	TQTc study	rich	995
D3820C00020	Japanese SAD and MAD	rich	1175
D3820C00025	Relative Bioavailability	rich	1582
D3820C00012	Ketoconazole DDI	rich	687
D3820C00015	Rifampin DDI	rich	546
D3820C00032	Diltiazem DDI	rich	1298
07-IN-NX003	Phase IIb Study in OIC	rich	479
D3820C00004	Phase III Study in OIC	sparse	1983
D3820C00005	Phase III Study in OIC	sparse	2057
Total			13,792

(Source: Applicant's Population PK Report, Table 2)

The pharmacokinetic structural model is shown in Figure 7.

Figure 7. Diagram of the applications naloxegol population pk model



(Source: Applicant's Population PK Report, Figure 7)

Covariate selection was performed with the following covariate inclusion steps shown in Table 7.

Table 7. Summary of Stepwise Covariate Selection – Forward Selection

	Covariate Added	OFV	ΔOFV	Comment
Step 0 Base Model	None	68303.493	--	
Step 1	+ P-gpD on Vc	68223.988	-79.505	(Reference: Step 0)
Step 2	+ Race-Asian on Vc	68102.929	-121.059	(Reference: Step 1)
Step 3	+ FORM on Vc	68025.260	-77.669	(Reference: Step 2)
Step 4	+ CrCL on Vc	67974.762	-50.498	(Reference: Step 3)
Step 5	+ P-gpH on CL	67946.135	-28.627	(Reference: Step 4)
Step 6	+ Sex on Vc	67906.376	-39.759	(Reference: Step 5)
Step 7	+ Race-(black) on CL	67881.366	-25.01	(Reference: Step 6)
Step 8	+ P-gpH on Vc	67848.300	-33.066	(Reference: Step 7)
Step 9	+ Age on Vc	67833.533	-14.767	(Reference: Step 8)
Step 10	+ P-gpD-CL	67801.424	-32.109	(Reference: Step 9)
Step 11– Final Model	+ BODD-Vc	67783.099	-18.325	(Reference: Step 10)
Step 12	+ Weight-CL	67772.792	-10.307	(Reference: Step 11)

Data source: \\usuwphdevcanda1\PM_1\nktr\Publishing\popPK files\CovrunSummary.csv
Abbreviations: BODD=Baseline opioid mean weekly dose; CL= clearance; CrCL=creatinine clearance; FORM=formulation; OFV=objective function value; ΔOFV=change in objective function value; P-gpD=p-glycoprotein inducer; P-gpH=p-glycoprotein inhibitor; Vc=volume of central compartment

(Source: Applicant's Population PK Report, Table 12)

Final pop PK parameter estimates are shown in Table 8.

Table 8. Parameter estimates for the base, full, and final population PK models.

	Estimate ± SE		
Parameter	**Base Model (Model 501)**	**Full Model**	**Final Model**
OFV	68303.493	67690.291	67783.099
Fixed Effects			
CL/F (L/h)	121 ± 3.44	125 ± 11.4	115 ± 3.41
C3DS-CL (L/h)	856 ± 76.3	356 ± 147	317 ± 117
C3HM-CL (L/h)	54.8 ± 2.92	80.5 ± 9.81	74.7 ± 5.88
LF1-CL (L/h)	122 ± 16.2	140 ± 20.4	110 ± 11.9
LF2-CL (L/h)	128 ± 18.4	141 ± 21.6	126 ± 17.1
Phase III-CL (L/h)	85.2 ± 2.2	76.2 ± 7.39	82.4 ± 2.21
Age on CL	NA	-0.196 ± 0.0838	NA
Weight on CL	NA	-0.401 ± 0.111	NA
CrCL on CL	NA	0.138 ± 0.0601	NA
ALT on CL	NA	-0.0428 ± 0.0353	NA
BODD on CL	NA	0.0858 ± 0.0318	NA
Sex on CL	NA	-0.0473 ± 0.0489	NA
Race-black on CL	NA	0.333 ± 0.0738	0.265 ± 0.0573
Race-Asian on CL	NA	-0.222 ± 0.0586	NA
Race-Other on CL	NA	0.381 ± 0.192	NA
Phase II on CL (L/h)	NA	-0.239 ± 0.123	NA
BTP1 on CL	NA	0.107 ± 0.103	NA
BTP2 on CL	NA	-0.0121 ± 0.0746	NA
LIR1 on CL	NA	0.445 ± 0.396	NA
C3HW on CL	NA	-0.0664 ± 0.0515	NA
C3DM on CL	NA	0.0506 ± 0.257	NA
C3DW on CL	NA	0.112 ± 0.121	NA
P-gpH on CL	NA	-0.337 ± 0.0525	-0.343 ± 0.0548
P-gpD on CL	NA	2.02 ± 1.18	2.14 ± 1.13
FORM on CL	NA	0.0711 ± 0.048	NA
Vc/F (L)	229 ± 22.2	168 ± 40.2	160 ± 27.4
PH3-Vc (L)	279 ± 23	233 ± 49.6	277 ± 52.4
Age on Vc	NA	-0.278 ± 0.0975	-0.209 ± 0.0848

Weight on Vc	NA	0.136 ± 0.164	NA
CrCL on Vc	NA	0.128 ± 0.059	0.109 ± 0.0485
ALT on Vc	NA	-0.0235 ± 0.0525	NA
BODD on Vc	NA	-0.0419 ± 0.0574	-0.107 ± 0.0385
Sex on Vc	NA	-0.147 ± 0.0636	-0.169 ± 0.0507
Race-black on Vc	NA	0.0878 ± 0.0766	NA
Race-Asian on Vc	NA	-0.505 ± 0.0646	-0.519 ± 0.0581
Race-Other on Vc	NA	0.23 ± 0.162	NA
Phase II on Vc	NA	-0.0448 ± 0.213	NA
BTP1 on Vc	NA	0.348 ± 0.174	0.267 ± 0.139
BTP2 on Vc	NA	0.175 ± 0.155	NA
LIR1 on Vc	NA	-0.0616 ± 0.104	NA
C3HW on Vc	NA	-0.183 ± 0.334	NA
C3DM on Vc	NA	-0.105 ± 0.0758	NA
C3DW on Vc	NA	1.53 ± 0.805	NA
P-gpH on Vc	NA	-0.269 ± 0.176	NA
P-gpD on Vc	NA	-0.238 ± 0.0727	-0.237 ± 0.075
FORM on Vc	NA	1.3 ± 0.469	1.37 ± 0.478
Q/F (L/h)	17.9 ± 0.916	18.4 ± 1.09	18 ± 1.17
Vp/F (L)	282 ± 15.2	267 ± 13.4	266 ± 13.7
KA (hr-1)	4.7 ± 0.481	4.99 ± 0.53	4.56 ± 0.468
KA2 (hr-1)	2.69 ± 0.334	15.2 ± 1.51	2.78 ± 0.41
K53 (hr-1)	0.406 ± 0.0141	0.408 ± 0.00996	0.416 ± 0.0117
F1splt	0.43 ± 0.0482	0.35 ± 0.0506	0.425 ± 0.0539
C3HS-S3	0.0798 ± 0.00685	0.122 ± 0.0118	0.124 ± 0.0122
Dose on Vc	-0.338 ± 0.0441	-0.294 ± 0.0377	-0.359 ± 0.0432
Dose on ka	0.146 ± 0.0583	0.209 ± 0.0593	0.143 ± 0.061
Dose on ka2	-0.333 ± 0.159	0.0197 ± 0.0888	-0.349 ± 0.169
Dose on Q	-0.163 ± 0.0468	-0.126 ± 0.0436	-0.129 ± 0.0441
Dose on Vp	-0.174 ± 0.0545	-0.165 ± 0.0441	-0.167 ± 0.047
IIV (ω)			
CL/F	0.491	0.482	0.477
Vc/F	0.507	0.485	0.512
Residual Error			
Proportional – Phase I & II	0.446 ± 0.00702	0.436 ± 0.00698	0.437 ± 0.007
Proportional – Phase III	0.566 ± 0.00961	0.565 ± 0.00958	0.564 ± 0.00955

Data source: \\usuwphdevcanda1\PM_1\nktr\Publishing\popPK files\Table13.ssc,
\\usuwphdevcanda1\PM_1\nktr\Publishing\popPK files\Run501.out,
\\usuwphdevcanda1\PM_1\nktr\Publishing\popPK files\Run501-full.out,
\\usuwphdevcanda1\PM_1\nktr\Publishing\popPK files\Run501-final.out

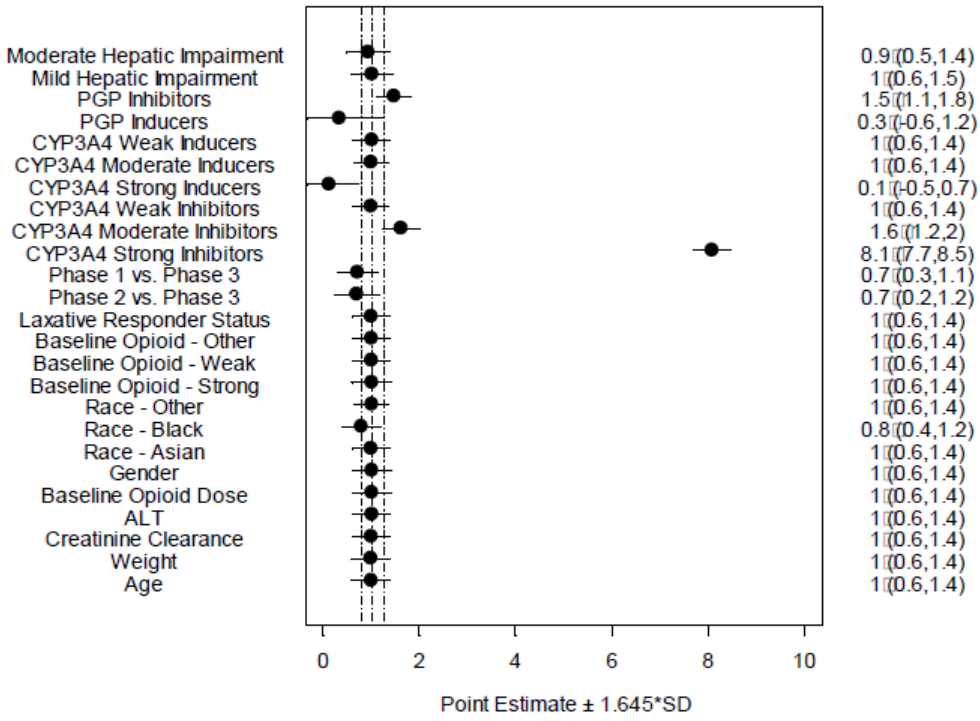
Abbreviations: ALT=alanine aminotransferase BODD=baseline mean weekly opioid dose; BTP1=Baseline opioid maintenance drug weak type; BTP2=Baseline opioid maintenance drug strong type; C3DM=Concomitant moderate inducer of CYP3A4; C3DS=concomitant strong inducer of CYP3A4; C3DW=Concomitant weak inducer of CYP3A4; C3HM=concomitant moderate inhibitor of CYP3A4; C3HS=concomitant strong inhibitor of CYP3A4; C3HW=concomitant weak inhibitor of CYP3A4; CrCL=creatinine clearance; CYP3A4=cytochrome P450 3A4; FORM=naloxegol formulation; LF1=mild hepatic impairment; LF2=moderate hepatic impairment; LIR1=Laxative inadequate responder; NA=not applicable; P-gpD=concomitant p-glycoprotein inducer; P-gpH=concomitant p-glycoprotein inhibitor; PH3=Phase III study

All models in this table have diagonal Ω structure and uses proportional residual error model unless specified otherwise.

(Source: Applicant's Population PK Report, Table 13)

Forest plots to show the magnitude of effect of each covariate on AUC are shown in Figure 8

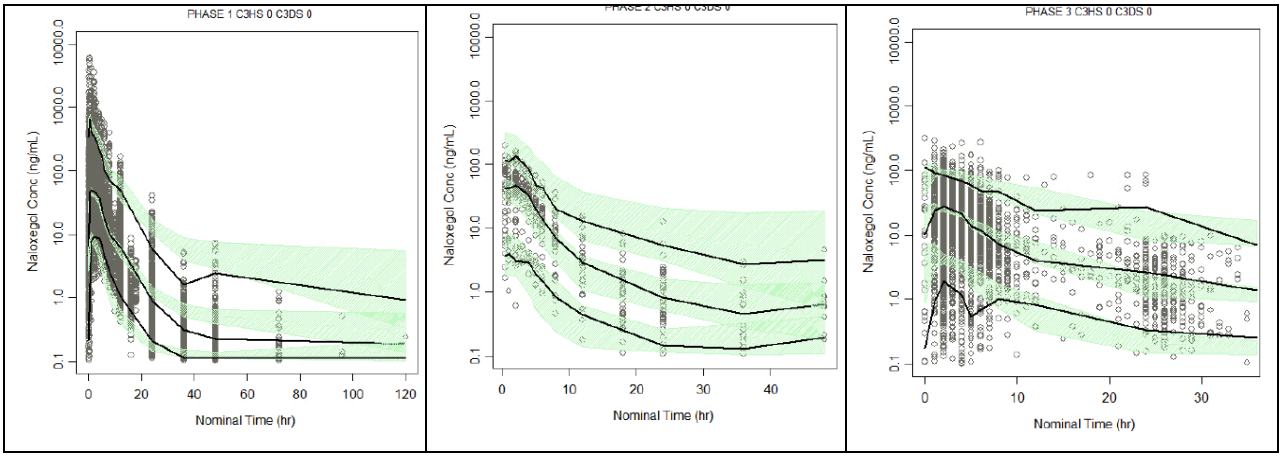
Figure 8. Forrest plot of covariate effects on the AUC of naloxegol.



(Source: Applicant's Population PK Report, Figure 14)

Model Diagnostic Plots are shown in Figure 9.

Figure 9. Visual predictive checks from the final population PK model for the phase 1 data (left panel), phase 2 data (middle panel), phase 3 data (right panel).



(Source: Applicant's Population PK Report, Appendix M)

Eta Plots for each of the covariates included in the base, full model, and final models are shown in Appendices E – K of the applicant's population PK report.

Reviewer's Comments:

When considering 1) the amount of data and data source (phase 1, phase 2, and phase 3) PK data, 2) the methods used to construct the model, and 3) the visual predictive check for the phase 3 data, the applicant's population model appears acceptable to predict AUC values in the phase 3 data to base exposure-response analyses on. With

regards to the reviewer's analysis, the population PK model is only used to obtain AUC values for each patient for exposure-response analyses. Results from the dedicated studies for renal impairment, hepatic impairment, and DDIs are the primary motivation for dosing adjustment in those populations.

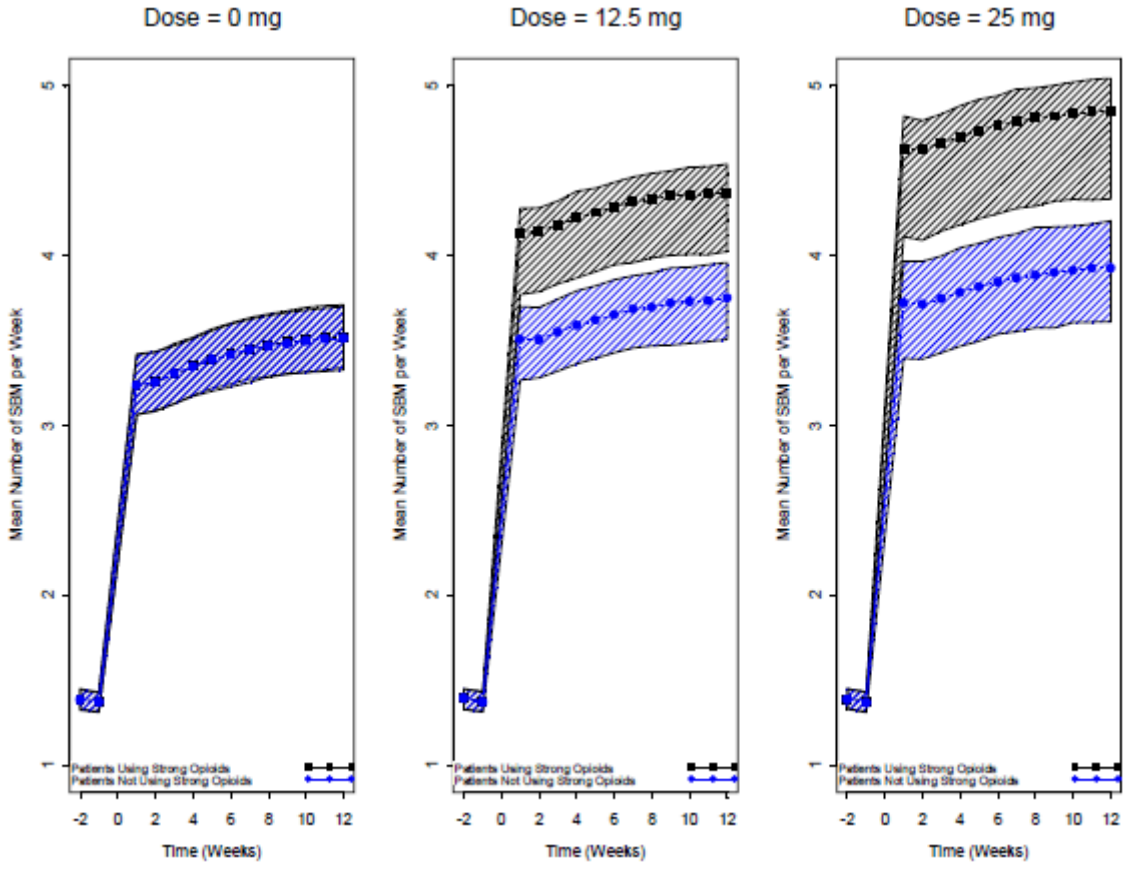
Based on the sponsor's model, the labeling statements regarding pharmacokinetics by gender, age, and race are acceptable.

3.3 Exposure-Response for Number of SBMs Daily:

The applicant conducted stochastic modeling of the SBM events in relation to exposure to the drug and other potential covariates such as age, BMI, baseline opioid daily dose, duration of opioid use, sex, race, baseline opioid maintenance type by potency, baseline laxative response, and baseline anticholinergic use.

The applicant concluded that there was an exposure-response for the occurrence of SBMs and that concomitant use of strong opioids was the only covariate that significantly influenced the prediction of response.

Figure 10. Effect of strong opioid use on model predictions by dose. The black shaded regions are for those taking strong opioid concomitantly. The blue regions are for those not taking strong opioids concomitantly.



(Source: Applicant's Exposure-Response for Efficacy Report, Figure 8)

Reviewer's Comments

The sponsor's exposure response analysis appears reasonable for capturing the effect of concomitant opioid use on the naloxegol effect on SBMs per week. Reviewer conducted independent exposure-response analysis for the efficacy primary endpoint. Reviewer concluded that a significant exposure-response curve is also present for the primary endpoint (see Section 4.4.1 for further details).

3.4 Dose/Exposure-Response for Safety:

The applicant evaluated dose/exposure-response for several types of adverse events, gastrointestinal, opioid withdrawal AEs, and blood pressure. Data were included from the on-treatment 12 week period of Trials 04 and 05.

3.4.1 Gastrointestinal AEs

The applicant evaluated only the occurrence of moderate and severe GI AEs related to abdominal pain, diarrhea, nausea, flatulence and vomiting over the 12 week treatment period of trials 04 and 05.

The applicant's final model was a function of dose, based on the lowest objective function value. Parameter estimates for this model are shown in

Table 9. Applicant's final model for predicted probability and odds ratio for GI AEs.

Dose group	Observed probability (%)	Estimated probability (%)	95% CI	Estimated odds ratio (95% CI)
Placebo	7.2	6.8	4.7-9.7	NA
12.5 mg	9.3	10.1	7.7-13.4	1.54 (0.95-2.49)
25 mg	15.2	14.8	11.9-18.4	2.46 (1.56-3.86)

CI=confidence interval; NA=not applicable

(Source: Applicant's Exposure-Response for Safety Report, Table 5)

Reviewer's Comments:

The applicant's model is a function of dose and accents the fact that the 25 mg dose group had a higher rate of gastrointestinal adverse events. This analysis is consistent with the Reviewer's analysis by naloxegol exposure.

3.4.2 Withdrawal AEs

While the applicant evaluated exposure response for withdrawal events, their conclusion was that there were too few events to conclude a relationship between exposure and opioid withdrawal. Numbers of patients with potential opioid withdrawal AEs and discontinuations due to potential opioid withdrawal are shown in Table and Table.

Table 10. Number (%) of patients with preferred terms potentially related to opioid withdrawal during the treatment period (12-week pool of studies 04 and 05 and study 08)

	12-week pool (Studies 04 and 05)			52-week safety study (Study 08)	
	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)	Usual care (N=270)	NGL 25 mg (N=534)
Any PT	**27 (6.1)**	**30 (6.8)**	**52 (11.7)**	**36 (13.3)**	**113 (21.2)**
Hyperhidrosis	1 (0.2)	2 (0.5)	13 (2.9)	1 (0.4)	17 (3.2)
Anxiety	5 (1.1)	7 (1.6)	7 (1.6)	4 (1.5)	17 (3.2)
Arthralgia	5 (1.1)	4 (0.9)	5 (1.1)	16 (5.9)	33 (6.2)
Drug withdrawal syndrome	1 (0.2)	2 (0.5)	5 (1.1)	0	2 (0.4)
Hot flush	2 (0.5)	2 (0.5)	4 (0.9)	3 (1.1)	6 (1.1)
Muscle spasms	3 (0.7)	3 (0.7)	3 (0.7)	8 (3.0)	17 (3.2)
Palpitations	1 (0.2)	3 (0.7)	3 (0.7)	1 (0.4)	2 (0.4)
Tremor	2 (0.5)	1 (0.2)	3 (0.7)	1 (0.4)	2 (0.4)
Rhinorrhea	0	1 (0.2)	3 (0.7)	1 (0.4)	4 (0.7)
Myalgia	0	0	3 (0.7)	1 (0.4)	3 (0.6)
Insomnia	3 (0.7)	1 (0.2)	2 (0.4)	5 (1.9)	15 (2.8)
Flushing	1 (0.2)	1 (0.2)	2 (0.4)	0	3 (0.6)
Cold sweat	0	1 (0.2)	2 (0.4)	0	1 (0.2)
Yawning	1 (0.2)	0	2 (0.4)	0	3 (0.6)
Feeling jittery	1 (0.2)	2 (0.5)	1 (0.2)	0	1 (0.2)
Chills	1 (0.2)	1 (0.2)	1 (0.2)	0	11 (2.1)
Restlessness	1 (0.2)	0	0	0	4 (0.7)
Tachycardia	1 (0.2)	0	1 (0.2)	0	3 (0.6)
Sneezing	0	0	0	2 (0.7)	2 (0.4)
Irritability	0	1 (0.2)	1 (0.2)	0	2 (0.4)
Muscle twitching	0	0	0	0	2 (0.4)

(Source: Applicant's Opioid Withdrawal and CV Risk Assessments Report, Table 1)

Table 11. Number (%) of patients with discontinuations due to AEs potentially related to opioid withdrawal (12-week pool in studies 04 and 05 and Study 08)

	12-week pool (Studies 04 and 05)			52-week safety study (Study 08)	
	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)	Usual care (N=270)	NGL 25 mg (N=534)
Any DAE	**6 (1.4)**	**0**	**9 (2.0)**	**Not applicable[a]**	**10 (1.9)**
Hyperhidrosis	1 (0.2)	0	4 (0.9)		3 (0.6)
Myalgia	0	0	2 (0.4)		1 (0.2)
Drug withdrawal syndrome	1 (0.2)	0	1 (0.2)		0
Yawning	1 (0.2)	0	1 (0.2)		0
Chills	0	0	1 (0.2)		3 (0.6)
Drug effect decreased	0	0	1 (0.2)		0
Feeling jittery	0	0	1 (0.2)		0
Drug dependence	0	0	1 (0.2)		0
Rhinorrhea	0	0	1 (0.2)		0
Night sweats	1 (0.2)	0	0		0
Restlessness	1 (0.2)	0	0		1 (0.2)
Palpitations	1 (0.2)	0	0		0
Tachycardia	1 (0.2)	0	0		0
Tremor	1 (0.2)	0	0		0
Flushing	1 (0.2)	0	0		0
Arthralgia	0	0	0		2 (0.4)
Anxiety	0	0	0		1 (0.2)

(Source: Applicant's Opioid Withdrawal and CV Risk Assessments Report, Table 3)

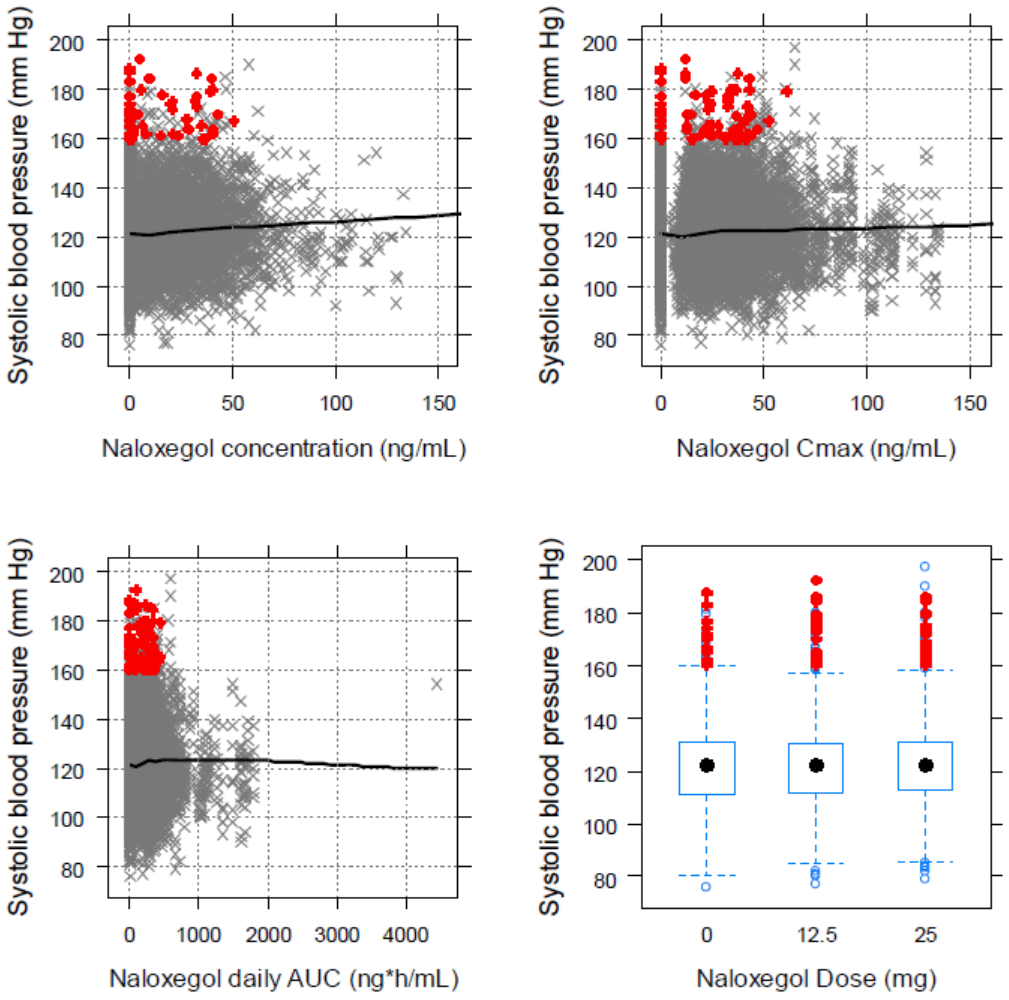
Reviewer's Comments:

While the numbers of potential withdrawal adverse events are small, there is still an almost 2 fold increase in the occurrence of these events in the 25 mg dose group compared to the 12.5 mg dose group. Additionally, no discontinuations due to withdrawal AEs were observed in the 12.5 mg dose group.

3.4.3 Systolic Blood Pressure:

The applicant evaluated the occurrence of high systolic pressure defined as SBP ≥ 160 and a change from baseline of ≥20 mm Hg (Figure 11). Based on this analysis, they concluded there was no effect of naloxegol on the systolic blood pressure.

Figure 11. SBP-naloxegol exposure response relationship over the 12-week treatment period. Red points indicate those individuals who met the applicant's criteria for an increase in systolic blood pressure.



(Source: Applicant's Exposure Response for Safety Report, Figure 6)

Reviewer's Comments: The sponsor 1) used a categorical analysis of blood pressure which reduces the power to detect an effect and 2) did not indicate the type of regression that is shown in their plots. Therefore, the reviewer's analysis evaluated a linear mixed effects analysis to ascertain whether any change in systolic blood pressure was observed with exposure.

4 REVIEWER'S ANALYSIS

4.1 Introduction

The reviewer's analysis is aimed at establishing whether or not exposure-response exists for the efficacy and safety of naloxegol in order to determine if the proposed dosing is reasonable.

4.2 Objectives

Analysis objectives are:

To evaluate exposure-response for the primary efficacy endpoint of response rate.

To evaluate exposure-response for safety events including gastrointestinal AEs, opioid withdrawal AEs, and blood pressure.

To evaluate the evidence of effectiveness for patients experiencing abdominal pain.

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 12.

Table 12. Analysis Data Sets

Study Number	Name	Link to EDR
Trial 04	*.xpt	\\Cdsesub1\evsprod\NDA204760\0000\m5\datasets\d3820c00004\analysis\adam\datasets
Trial 05	*.xpt	\\Cdsesub1\evsprod\NDA204760\0000\m5\datasets\d3820c00005\analysis\adam\datasets
Population PK	*.xpt	\\Cdsesub1\evsprod\NDA204760\0000\m5\datasets\population-pk\analysis\legacy\datasets
ISS-ISE	*.xpt	\\Cdsesub1\evsprod\NDA204760\0000\m5\datasets\ise-iss\safeffph3\analysis\adam\datasets

4.3.2 Software

S-plus (Tibco) was used to perform graphical analysis and data management.

4.3.3 Models

No changes were made to the applicant's population PK or PK/PD models.

4.4 Results

4.4.1 Exposure – Response for Efficacy:

Based on the applicant's primary efficacy analysis (Figure 5), there is an evident trend in dose-response for the efficacy of naloxegol with a modest increase in response rates between 12.5 and 25 mg dose groups. Response rates for the primary endpoint in study 04 are 29.4%, *40.8%, *44.4% for placebo, 12.5 and 25 mg arms. Response rates for the replicate study 05 are 29.3%, 34.9%, *39.7% for placebo, 12.5 and 25 mg arms, where the * denotes statistical significance indicating that the lower dose of 12.5 mg did not meet the statistical significance in trial 05. The 25 mg dose is most effective and the efficacy conclusions are consistent across all secondary endpoints

(response rate in LIR subgroup, time to first post-dose SBM, and mean number of days per week where SBM were > 1). Doses as high as 50 mg were studied in phase 2. However, adverse events prevented this dose from being studied in the phase 3 trials.

Exposure-response analysis for the primary efficacy endpoint (Figure 2) showed a significant relationship between exposures and response which is consistent with the dose response, suggesting that higher exposures lead to better response. The significant exposure-response analysis provides supportive evidence of effectiveness for the naloxegol in the treatment of opioid induced constipation. Moreover, the shallow exposure-response analysis also indicates that lower exposures compared to that observed with 25 mg may not result in a meaningful loss of efficacy.

4.4.2 Exposure – Response for Safety:

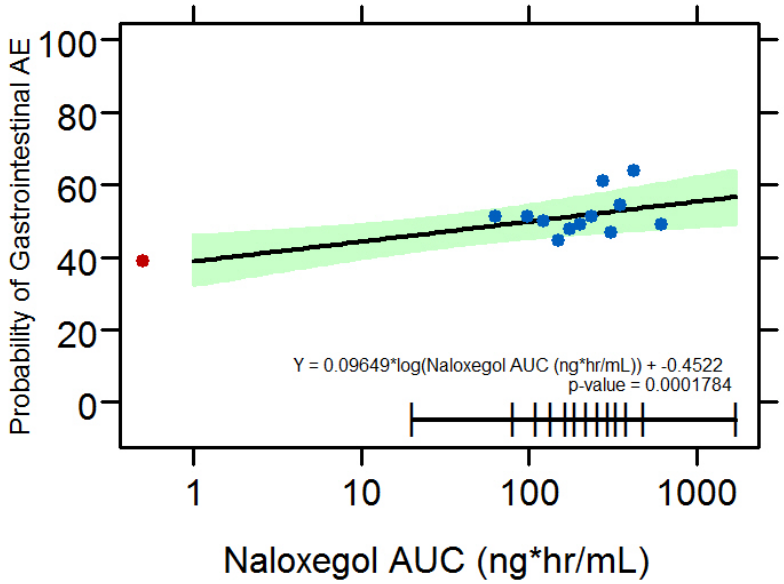
4.4.2.1 Gastrointestinal Adverse Events:

Both dose-response and exposure-response relationships were evident for gastroinstestinal related adverse events (Table and Figure).

Table 13. There is dose-response for the number of individuals with all-grade gastroinstestinal related adverse events for studies 04 and 05 combined.

	Placebo	12.5 mg	25 mg
	N=444	N=441	N=446
Abdominal Pain	25	43	71
Diarrhea	19	25	41
Nausea	20	29	36
Flatulence	11	13	26
Vomiting	13	10	20
Upper Abdominal Pain	7	8	17

Figure 12. Exposure-response is evident for gastrointestinal related adverse events. The logistic regression and prediction interval is shown by the solid line and shaded region. The analysis was conducted on placebo and naloxegol data simultaneously, assuming placebo concentrations of naloxegol were zero. Data points are the probability for the placebo (red) and naloxegol (blue) exposure bins, denoted by the bars at the bottom of the plot.



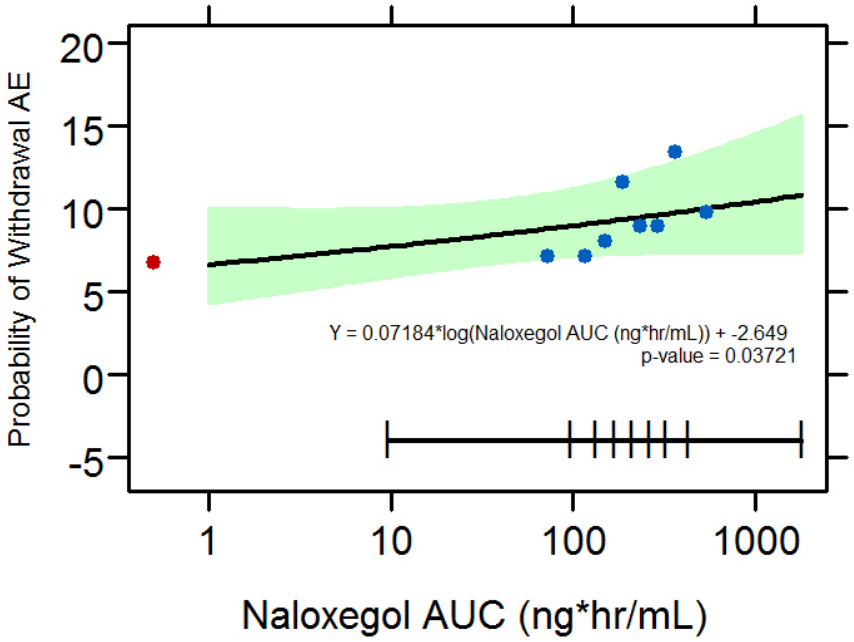
Based on these results, abdominal pain was subsequently evaluated by severity (Figure 1) and exposure-response for adverse events for moderate & severe and severe AEs was considered to be shallow. Dose-response was apparent for discontinuations due to withdrawal events (Table and Table), but the analysis was limited due to the small number of discontinuations due to withdrawal AEs.

4.4.2.2 Withdrawal AEs

The occurrence of withdrawal AEs were shown to increase with increasing naloxegol dose (Table).

Exposure-response for withdrawal was evaluated by logistic regression and the results are shown in Figure 13. There is a significant, but shallow, relationship for increasing occurrence of potential withdrawal AEs and naloxegol exposure. This relationship is consistent with the dose response findings.

Figure 13. Exposure-response for the occurrence of withdrawal AEs. The logistic regression and prediction interval is shown by the solid line and shaded region. The analysis was conducted on placebo and naloxegol data simultaneously, assuming placebo concentrations of naloxegol were zero. Data points are the probability for the placebo (red) and naloxegol (blue) exposure bins, denoted by the bars at the bottom of the plot.



4.4.2.3 Blood Pressure:

Linear Mixed Effects modeling were performed on the phase 3 data from trials 04 and 05. Additionally a separate analysis was performed for patients in the QT study that received doses as high as 150 mg, for the supra-therapeutic dose. The results of these analyses are shown in Table 14 and indicate a difference in response based on whether the individual was an opioid-induced constipation patient or healthy subject. Healthy subjects appeared to show no change in blood pressure; whereas, patients may experience a very slight increase in blood pressure.

Table 14. Results from linear mixed effects analysis suggest that the slight blood pressure increase is specific to patients and not healthy subjects.

	% Change from Baseline at 25 mg Cmax	mmHg Change at 25 mg Cmax	p-value
Studies 04, 05			
Diastolic BP	1.61	1.2	0.0096
Systolic BP	1.85	2.3	0.0008
QT Study			
Diastolic BP	-2.41	-1.8	0.08
Systolic BP	-0.73	-1.17	0.5665

Further review of blood pressure and CV AEs was conducted by the Division of Cardiology and Renal Products (see the review in DARRTS by Dr. Preston Dunnmon, 4/15/2014). Their conclusion was:

> "OXN appears to be associated with elevations of both SBP and DBP in patients previously treated (presumably for hypertension, and hypertensive AEs occurred. Of the nine patients experiencing an SMQ-

based CV AE and opioid withdrawal symptoms in the overall population (Group C) during any study period, three of the nine experienced blood pressure elevations in close proximity to OXN dosing, one of which was a hypertensive crisis. There were no concomitant AEs involving BP elevation with withdrawal symptoms in any comparator group"

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
EfficacyExpResp2.ssc	Analysis of TTE for withdrawal AEs, exposure-response for withdrawal AEs and subgroup efficacy analysis for those patients with opioid withdrawal	..\PM Review Archive\ 2014\Naloxegol_NDA204760_JCE\ER Analyses\
AbPain2.ssc	Analysis of TTE for abdominal pain, exposure-response for abdominal pain AEs and subgroup efficacy analysis for those patients with abdominal pain	..\PM Review Archive\ 2014\Naloxegol_NDA204760_JCE\ER Analyses\

Physiological-based Pharmacokinetic Modeling Review

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	NDA 204760
Drug Name	Naloxegol (NKTR-118)
Proposed Indication	For the treatment of Opioid-Induced constipation
Clinical Division	CDER/ODEIII/DGIEP
PBPK Consult request	Sandhya Apparaju Ph.D.; Shang, Elizabeth, Ph.D.
Primary PBPK Reviewer	Yuzhuo Pan, Ph.D.
Secondary PBPK Reviewer	Ping Zhao, Ph.D
Sponsor	ASTRAZENECA PHARMACEUTICALS LP

1. Objectives

The main purpose of this review memo is to review sponsor's physiologically-based pharmacokinetic (PBPK) report entitled "Physiologically Based Pharmacokinetic Modeling using SimCYP (version 12) to Evaluate the Systemic Exposure of Naloxegol in the Presence of CYP3A Inhibitors" [1] in NDA204760.

2. Background

2.1. Regulatory history on PBPK submission

Naloxegol (NKTR-118) is an orally administered, antagonist of μ-opioid receptor being developed for the treatment of opioid-induced constipation (OIC). Naloxegol is a PEGylated derivative of naloxone and is manufactured as the oxalate salt. PEGylation reduces naloxegol passive permeability and also renders the compound a substrate for the P-glycoprotein transporter (P-gp), limiting its penetration into the brain [2]. Given its mode of action as a peripheral μ -opioid receptor antagonist, naloxegol binds to μ-opioid receptors within the gastrointestinal tract. It treats the causes of long term OIC by increasing gastrointestinal motility, hypertonicity and decreasing fluid absorption. Sponsor proposed dose regimen is oral dose of 12.5 mg and 25 mg once daily (q.d.) for OIC.

A PBPK model was developed by the sponsor as part of the NDA submission [2]. The primary objectives of this PBPK submission were to predict the effect of moderate CYP3A inhibitors (ciprofloxacin, erythromycin, fluconazole, and verapamil) or weak CYP3A inhibitors (alprazolam, fluvoxamine, amlodipine, atorvastatin and cimetidine) on naloxegol exposure. After initial review of the report, an information request was sent to the sponsor on Oct 25, 2013 (10252013IR, Section 6.2.1). On Nov 14, 2013, sponsor submitted additional information to address issues raised in 10252013IR [3]. The second information request was sent on April 28, 2014 (04282014IR, Section 6.2.2). On May 1, 2014, sponsor submitted requested data [4].

2.2. Highlight of drug absorption and disposition

Table 15. Summary of naloxegol's absorption, distribution, metabolism and excretion (ADME) [2]

Absorption	Following oral administration, naloxegol is rapidly absorbed, with peak concentrations (Cmax) achieved at less than 2 hours. In the majority of subjects, a secondary plasma concentration peak of naloxegol was observed approximately 0.4 to 3 hours after the first peak, possibly due to enterohepatic recirculation.
Distribution	The mean apparent volume of distribution during the terminal phase (Vz/F) in healthy volunteers ranged from 968 to 2140 L across dosing groups and studies. Plasma protein binding of naloxegol in human was low and the fraction unbound ranged from 80% to 100%.
Metabolism	Primary route of drug elimination is through extensive metabolism by CYP3A.
Excretion	Following oral administration of radio-labelled naloxegol, 68% and 16% of total administered dose were recovered in the feces and urine, respectively. Parent naloxegol excreted in the urine accounted for less than 6% of the total administered dose. Thus renal excretion is a minor clearance pathway for naloxegol.

Naloxegol is a substrate of CYP3A enzyme and a substrate of P-gp transporter. Co-administration of dual P-gp/ strong or moderate CYP3A inhibitors, or strong CYP3A inhibitors significantly increases naloxegol plasma concentrations. The submitted PBPK modeling report [1] and additional information requested by the Office of Clinical Pharmacology [3,4] addressed the key questions on whether PBPK model predicts changes in naloxegol exposure when the drug is co-administered with various CYP3A inhibitors or inducers.

3. Methods

SimCYP® (V12.1, Sheffield, UK) [5,6] was used by the sponsor to construct and verify PBPK model. Final model input parameters and their sources are summarized in Appendix Tables A1, A2 and A3. PBPK models of ketoconazole (400 mg once daily), rifampin, diltiazem and metabolite, quinidine and metabolite were from software

model library. Quinidine model was modified by incorporating a reversible Ki of P-gp (0.43 □M) [7]. Unless otherwise stated, all simulations used the "sim-Healthy Volunteer" population from software system model library, and were conducted in 10 trials with 10 subjects per trial.

Naloxegol PBPK modeling followed three steps:

3.1. Model building

Sponsor built two PBPK models: minimal and full PBPK models [8-10]. The key differences aresummarized in Table 2. Results of in vitro ADME experiments and physicochemical properties, and PK studies were used in naloxegol model building. Metabolism was defined as solely by CYP3A, and in vivo oral clearance of approximately 150 L/h was used to optimize drug metabolism in the liver and in the intestine using software's retrograde method [5]. Sponsor provided cross study comparison of naloxegol clearance from various studies to substantiate the use of 150 L/h (**Appendix Figure 1**).

Table 16. Summary of sponsor's two PBPK models

	Mini-PBPK model	**Full PBPK model**
Objective	DDI prediction	Justification of P-gp contribution
Absorption	First order absorption	Advanced Dissolution, Absorption, and Metabolism model (ADAM)
Distribution	Minimal PBPK with a "Single Adjusting Compartment" (SAC)	Full PBPK
Metabolism	CYP3A4 (100%)	CYP3A4 (100%)
Transport	Not available	P-gp efflux in small intestine and liver (permeability limited models)
Parameters	Appendix Tables 1 & 2	Appendix Tables 1 & 3

3.2. Model verification

The following clinical drug-drug interaction (DDI) studies with various CYP3A inhibitors and inducers were used to verify naloxegol PBPK models (Table 3). These studies evaluated the effect of CYP3A modulators on naloxegol exposure after single oral dose of naloxegol of 25 mg [1].

Table 17. CYP3A4 and P-gp modulators studied in the DDI studies and their effect co-administrated with Single oral 25mg naloxegol.

Study ID	**Perpetrator (Dose)**	**Mechanism**
D3820C00012	ketoconazole 400mg q.d. for 5 days (naloxegol on day 4)	Strong CYP3A inhibitor; P-gp inhibitor
D3820C00032	extended-release diltiazem 240 mg q.d. for 5 days (naloxegol on day 4)	Moderate CYP3A inhibitor; P-gp inhibitor
D3820C00011	quinidine 600mg single dose coadministered with naloxegol	weak CYP3A inhibitor; P-gp inhibitor
D3820C00015	rifampin 600mg q.d. for 13 days (naloxegol on day 13)	strong CYP3A inducer; P-gp inducer

3.3. Model Prediction

The sponsor conducted simulations using both mini-PBPK and full PBPK models to predict the effect of moderate CYP3A inhibitors (ciprofloxacin, erythromycin, fluconazole, and verapamil), weak CYP3A inhibitors (alprazolam, fluvoxamine, amlodipine, atorvastatin and cimetidine), or moderate CYP3A inducer efavirenzon naloxegol exposure after a single oral dose of 25 mg [1,5]. The input parameters of these inhibitors were provided in sponsor's PBPK report, with modifications of the software library models summarized in **Appendix Table 4** [1]. Inhibitor PBPK models were verified via simulations using probe substrates based on literature findings. The input parameters of

efavirenz was based on those reported in reference [11], along with published values for pKa (10.2; [12]) and unbound plasma protein binding (0.029; [13]). Efavirenz model parameters are summarized in **Appendix Table 5**.

4. Results

4.1. Can the effect of various CYP3A modulators on the exposure of naloxegol be predicted using PBPK?

The constructed minimal PBPK model of naloxegol reasonably described the observed PK profiles of naloxegol [1]. The model was further verified using clinical drug-drug interaction data when the drug was co-administered with ketoconazole (a strong CYP3A inhibitor and a P-gp inhibitor), rifampin (a strong CYP3A inducer and a P-gp inducer), diltiazem (a moderate CYP3A inhibitor and a P-gp inhibitor), or quinidine (a strong P-gp inhibitor and a weak CYP3A inhibitor). As shown in **Table 4**, PBPK reasonably predicted geometric mean AUC ratios and Cmax ratios by inhibitors ketoconazole, diltiazem, and quinidine. The observed and PBPK predicted geometric mean AUC ratio by inducer rifampin were 0.11 and 0.24, respectively. The apparent under-estimation of the effect on naloxegol clearance (over estimation of exposure) by rifampin may be attributed to inadequacy of library's rifampin PBPK model that has been shown to underestimate its effect on clearance of other CYP3A substrates [15,16].

Table 18.PBPK predicted and observed geometric mean naloxegol exposure ratios after single oral naloxegol dose (25 mg)
(See **Appendix Table 6** for details)

	AUC Ratio			Cmax Ratio		
Inhibitor	**Simulated**	**Observed**	**Sim/Obs**	**Simulated**	**Observed**	**Sim/Obs**
Ketoconazole	13.14	12.85	1.02	7.75	9.58	0.81
Diltiazem	2.80	3.41	0.82	2.28	2.85	0.80
Rifampin	0.24	0.11	**2.18**	0.27	0.25	1.08
Quinidine	1.23	1.39	0.88	1.87	2.47	0.76

Sponsor's draft label indicates tha

The statement was supported in part by the PBPK simulated effect of various moderate and weak CYP3A inhibitors that have been co-administrated with naloxegol in phase 3 studies [1]. As shown in **Table 5**, the simulated geometric mean AUCR of naloxegol by moderate CYP3A inhibitors fluconazole, verapamil, erythromycin and ciprofloxacin are 2.8, 2.2, 4.6, and 1.1-fold, respectively; the simulated geometric mean AUCR values of naloxegol by weak CYP3A inhibitors alprazolam, amlodipine, atorvastatin, fluoxetine and cimetidine are 1.0, 1.2, 1.1, 1.3, and 1.4-fold, respectively. Table 5 also includes the predicted effect of a moderateCYP3A inducer efavirenz on naloxegol exposure. The simulated geometric mean AUCR of single oral dose of naloxegol by efavirenz is 0.49, suggesting 25 mg naloxegol with a moderate CYP3A inducer would achieve similar naloxegol exposure to that after 12.5 mg naloxegol alone.

Table 19. Predicted naloxegol geometric mean exposure ratios using minimal PBPK of naloxegol; (See Minimal PBPK predictions from Appendix Table 7 **for details)**

	AUC Ratio	Cmax Ratio
Moderate CYP3A inhibitors[$]		
Fluconazole	2.8	2.4
Verapamil	2.2	2.0
Erythromycin 1[&]	3.5	2.8
Erythromycin 2[&]	4.6	3.4
Ciprofloxacin	1.0	1.0
Weak CYP3A inhibitors[$]		
Alprazolam	1.0	1.0
Amlodipine	1.2	1.2
Atorvastatin	1.1	1.1
Fluoxetine	1.3	1.2
Cimetidine	1.4	1.3
Moderate CYP3A inducer[$]		
Efavirenz	0.49	0.51

[$] Defined according to FDA draft drug interaction guidance (2012). [&] Two doses have been used in this simulation: 1. 250 mg once every 6 hours for 5 days; 2. 400 mg once every 6 hours for 5 days (See Appendix Table 5)

4.2. Potential effect of P-gP inhibition

In response to FDA's information request regarding to the potential effect of P-gp on the disposition of naloxegol and consequently DDI related to P-gp (**Appendix 1**), sponsor explored the model construct/variation by incorporating P-gp mechanisms and additional simulations using a full PBPK model [3]. The simulated effect of ketoconazole, rifampin, and diltiazem appeared to be less than that simulated using minimal PBPK model of naloxegol and that observed in vivo (**Appendix Table 8 and Table 4**) [3]. For quinidine, simulation using full PBPK model of naloxegol shows similar prediction as that using minimal PBPK model [3]. Together, it appears that CYP3A metabolism is "the dominate factor in naloxegol disposition, and that contribution from P-gp is minor", and the effect observed for quinidine seems to reflect a weak CYP3A inhibition mechanism by quinidine [3].

In response to agency's comment on using PBPK to evaluate the effect of naloxegol on central nervous system (CNS) [3], sponsor provided the following justification. In quinidine-naloxegol study (Study D3820C00011), sponsor specifically investigated the potential for change in CNS distribution of naloxegol in the presence of P-gP inhibition. This study used inhibition of morphine-induced miosis as a biomarker of central opioid antagonism. Coadministration of naloxegol and quinidine did not antagonize morphine-induced miosis, indicating that P-gp inhibition does not increase naloxegol CNS distribution at clinically relevant doses. Therefore, co-administration of a P-gp inhibitor does not seem to affect the CNS distribution of naloxegol.

5. Conclusion

The sponsor's PBPK model reasonably predicted the observed effect of various CYP3A modulators. The simulations confirmed the predominant contribution of CYP3A metabolism for naloxegol, and predicted the effect of other moderate or weak CYP3A inhibitors, and a moderate CYP3A inducer on naloxegol exposure.

6. Appendices

6.1. **Abbreviations**

ADAM: Advanced dissolution, absorption, and metabolism model; ADME: absorption, distribution, metabolism, and excretion; b.i.d.: twice daily dosing; B/P: blood to plasma ratio; AUC: area under the concentration-time profile; AUCR: the ratio AUC of the substrate drug in the presence and absence of the perpetrator; B/P: blood to plasma ratio; Cmax, maximal concentration in plasma; CmaxR: the ratio of Cmax of the substrate drug in the presence or absence of the perpetrator; CL: clearance; CL_{int}: intrinsic clearance; CNS: Central nervous system; DDI: drug-drug interaction; F: bioavailability; Fa: fraction absorbed; Fg: fraction that escapes intestinal metabolism; fmj fraction of total clearance mediated by j CYP isoform or renal elimination; fp: fraction unbound in plasma; fu,mic: fraction unbound in microsomes; fu,gut: apparent unbound fraction in enterocytes; GI: gastrointestinal; IR: immediate release formulation; ka: first order absorption rate constant; Ki: reversible inhibition constant; LogP: logarithm of the octanol-water partition coefficient; NA: not applicable; ND, not determined; NDA: new drug application; OIC: opioid-induced constipation; Obs: Observed; P_{eff}, passive permeability; $P_{eff,man}$: Human jejunum permeability; PBPK: Physiological-based Pharmacokinetic; PEG: polyethylene glycol; P-gp: P-glycoprotein; q.d.: once daily dosing; Q_{gut}: a hypothetical flow term for the intestine absorption model; Sim: Simulated; Tmax: time at maximal concentration in plasma; V_{ss}: volume of distribution at steady state; Vz: apparent volume of distribution during the terminal phase.

6.2. **Information Requests**

4.3.1.1 6.2.1. Oct 25 Information Request (10252013IR)

4.3.2

"We conducted initial review of your PBPK study report "Physiologically Based Pharmacokinetic Modelling using SimCYP (version12) to Evaluate the Systemic Exposure of Naloxegol in the Presence of CYP3A Inhibitors". You should address the following comments by xx, 2013.
1. Construction of naloxegol PBPK model:

1.1. Hepatic clearance was obtained via retrograde calculation based on PK data from the "no inhibitor" arm of drug-drug interaction trial with ketoconazole. Have you considered using other, stand-alone oral PK data to construct naloxegol PBPK model? How does model simulated PK profile compare to the observed data from these other phase I trials?
1.2. Hepatic clearance was assumed to be predominantly contributed by CYP3A metabolism. Have you considered the contribution of P-gp to the biliary secretion of naloxegol? this assessment requires metabolite profiling data from your human mass balance study (Study D3820C00001). .
1.3. Renal clearance reported in mass balance study (study D3820C00001) was 6.96 L/h. In Table 1 of the PBPK report, the input for renal clearance was 4.2 L/h (based on study D3820C00009). Please justify the selection of renal clearance value.
1.4. Some CYP3A modulators are known to affect P-gp. Therefore, full PBPK model accounting for P-gp contribution should be developed for Naloxegol (see 1.1 above on potential contribution of P-gp to hepatic clearance), and inhibitor/inducer models should be updated with P-gp inhibition/induction mechanisms.
2. Verification of naloxegol PBPK model with available DDI data
2.1. Simulations of known DDI should be conducted using updated naloxegol and inhibitor/inducer models.
3. Application of the updated naloxegol PBPK model
3.1. Simulations of untested DDI scenarios with other inhibitor/inducers should be conducted using updated naloxegol model. Potential P-gp inhibition/induction mechanism should be considered for the interacting drugs.
3.2. We noticed that the incidence of headache doubled when ketoconazole, a P-gp inhibitor was co-administered in the dedicated DDI study with ketoconazole. Because naloxegol may target receptors in the brain, we recommend you use your PBPK model to evaluate potential effect of P-gp inhibition on brain drug exposure.
4. Please provide the updated files used to generate the final PBPK simulations (e.g. drug model files, population files, and workspace files, such as .cmp, .lbr, and .wks). The model files should be executable using SimCYP software Version 12.2. These files may be submitted via CD."

4.3.2.1 6.2.2. Apr 28, 2014 Information Request (04282014IR)

Please simulate the effect of a moderate CYP3A inducer efavirenz on naloxegol PK.
Design: Oral administration of efavirenz 400 mg once daily for 14 days, oral administration of a single dose of naloxegol (25 mg) on day 14.
Naloxegol model: Use the minimal PBPK model of naloxegol in your report dated 6/28/2013 for this simulation.
Efavirenz model: Refer to Redic et al (2011, reference 1) for the establishment/modification of efavirenz model in Simcyp, and conduct simulation with and without induction effect by efavirenz on gut CYP3A (see Mouly 2002, reference 2).
All simulations should be conducted in Simcyp v12 in your PBPK report submitted on 6/28/2013. Besides simulation results and description of efavirenz model development, please include relevant PBPK model files executable by FDA reviewers (e.g., .cmp, .wks, .lbr) in your submission. Please submit these information by end of Thursday, May 1, 2014.
References:
1. Rekic (2011). In silico prediction of efavirenz and rifampicin drug-drug interaction considering weight and CYP2B6 phenotype. Br J Clin Pharmacol. 71:536-543, 2011.
2. Mouly (2002). Hepatic but not intestinal CYP3A4 displays dose-dependent induction by efavirenz in humans. Clin Pharmacol Ther. 72:1-9, 2002.

6.3. **Appendix Tables and Figures**

Appendix Table 1. Physicochemical parameters of Naloxegol for PBPK model

Input parameter	*Value*	*Unit*	*Comment*
MW	652	g/mol	Study LS-2009-604
LogP	1.43		Study LS-2009-604
Compound Type	Diprotic base		Study LS-2009-604
pKa	8.45, 9.48		Study LS-2009-604
Dosage form	Immediate release tablet of 25 mg commercial formulation		

Appendix Table 2. Input parameters of Naloxegol for minimal PBPK model using SimCYP (V12)

Parameter	Value	Unit	Comment
Absorption			
Absorption Model	First order		Study Report [1]
fa	0.649	fraction	Predicted by SimCYP
ka	0.338	hr^{-1}	Predicted by SimCYP
Papp Caco-2 permeability	4.55	10^{-6} cm/s	study RD00001771[2]
Distribution			
B/P (blood to plasma ratio)	1	assumed	B/P of 1.3 predicted in SimCYP, B/P of 0.65 - 0.77 and 0.52 – 0.63 observed in rat (study 192617) and dog (study KKD001) respectively.
fu plasma	0.958	fraction	study LS-2007-024 [2]
Predicted V_{ss}	2.0	L/kg	Predicted using SimCYP Roger and Rowland method (Method 2). Vss of 2.44, 3.14, 4.66 L/kg observed in cynomolgus Monkey (study LS-2007-37) Sprague Dawley rat (study 3504LR) and beagle dog (study LS-2005-30) respectively. Summary of clinical pharmacology [2], prediction method according to references [10,11]
VSAC	1.33	L/kg	Estimated to fit targeted profile
Metabolism/Excretion			
CLpo	150	L/h	Study D3820C00012[2]
$F_{u,gut}$	1		Software default value
fumic	1		Software default value
CYP3A4 CLint	0.267	µL/min/pmol protein	Retrograde calculation
CL_{renal}	4.74	L/h	Study D3820C00009 and summary of clinical pharmacology [2]
Interaction			
CYP2D6 ki	42.3	µM	

Appendix Table 3. . Input parameters of Naloxegol for full PBPK model using SimCYP (V12)

Parameter	Value	Unit	Comment
Absorption	Advanced Dissolution, Absorption and Metabolism (ADAM) Model		Response to IR [3]
Papp Caco-2 permeability(6.5:7.4)	4.55	10^{-6} cm/s	study RD00001771
Peff,man Duodenum	3.5	10^{-4} cm/s	Response to IR [3]
Peff,man Jejunum I	3.5	10^{-4} cm/s	Response to IR [3]

Peff,man Jejunum II	3.5	10^{-4} cm/s	Response to IR [3]
Peff,man Ileum I	0.82	10^{-4} cm/s	Response to IR [3]
Peff,man Ileum II	0.82	10^{-4} cm/s	Response to IR [3]
Peff,man Ileum III	0.82	10^{-4} cm/s	Response to IR [3]
Peff,man Ileum IV	0.82	10^{-4} cm/s	Response to IR [3]
Peff,man colon	0.82	10^{-4} cm/s	Response to IR [3]
Formulation	Solution		
Distribution	Full PBPK		
B/P (blood to plasma ratio)	1	assumed	B/P of 1.3 predicted in SimCYP, B/P of 0.65 - 0.77 and 0.52 – 0.63 observed in rat (study 192617) and dog (study KKD001) respectively.
fu plasma	0.958	fraction	
Predicted V_{ss}	2.0	L/kg	
Prediction method	Method2		
Kp Scalar	1		Default
Liver model	Permeability limited		
Metabolism/Excretion			
CLpo	150	L/h	Study D3820C00012
$F_{u,gut}$	1		Software default value
CYP3A4 CLint	0.267	µL/min/pmol protein	Retrograde calculation
CL_{renal}	4.74	L/h	Study D3820C00009 and summary of clinical pharmacology [2]
fumic	1		
Biliary Clearance	Transporter Kinetics		Set up for P-gp
Interaction			Response to IR [3]
CYP2D6 ki	42.3	µM	
Transport			Response to IR [3]
Intestine P-gp Clint,T	2.5	µL/min	
Liver			
CLpd	0.1	mL/min/million hepatocytes	
P-gp Jmax	0.025	pmol/min/million cells	
P-gp Km	0.01	µM	

Appendix Table 4. Changes made by the sponsor for additional inhibitor drugs on software library drug models

Inhibitor name	Changes made	references
Alprazolam	CYP3A4 Ki = 25 □M	Bohets H, Lavrijsen K, Hendrickx J, van Houdt J, van Genechten V, Verboven P, Meuldermans W, Heykants J. Identification of the cytochrome P450 enzymes involved in the metabolism of cisapride: in vitro studies of potential co-medication interactions. Br J Pharmacol. 129:1655-67, 2000
	CYP3A4 Ki=67 □M; CYP3A4 MBI Kapp= 5.26 □M	Mayhew BS, Jones DR, Hall SD. An in vitro model for predicting in vivo inhibition of cytochrome P450 3A4 by metabolic intermediate complex formation. Drug Metab Dispos.2000; 28:1031-7
Amlodipine	Fu=0.07; Vss = 26 L/kg; CLpo = 24.8 L/h	UWDIDB
	CYP3A4 Ki = 20.0 □M	Ma B, Prueksaritanont T, Lin JH Drug interactions with calcium channel blockers: possible involvement of metabolite-intermediate complexation with CYP3A. Drug Metab Dispos. 2000 28:125-30.
	CYP3A4 MBI Kapp = 3.30 □M; kinact=2.34 /h	Zimmerlin A, Trunzer M, Faller B. CYP3A time-dependent inhibition risk assessment validated with 400 reference drugs. Drug Metab Dispos. 2011,39:1039-46.
Atorvastatin	Mol Weight =558.2 g/mol logP = 4.22; pKa = 4.3	Chen C, Mireles RJ, Campbell SD, Lin J, Mills JB, Xu JJ, Smolarek TA. Differential interaction of 3-hydroxy-3-methylglutaryl-coa reductase inhibitors with ABCB1, ABCC2, and OATP1B1. Drug Metab Dispos. 2005; 33: 537-46
	B/P = 1.0	Lennernäs H. Clinical pharmacokinetics of atorvastatin. Clin Pharmacokinet. 2003; 42:1141- 60
	Fu=0.02; Caco-2 permeability =28.410E-06cm/s; CLpo=121.8 L/h	UWDIDB
	CYP3A4 Ki = 0.6 □M	Fujino H, Yamada I, Shimada S, Yoneda M, Kojima J. Metabolic fate of pitavastatin, a new inhibitor of HMG-CoA reductase: human UDP-glucuronosyltransferase enzymes involved in lactonization. Xenobiotica. 2003; 33: 27-41.
Cimetidine	Mol Weight = 252.34 g/mol; log P = 0.48; pKa = 6.8	Jantratid E, Prakongpan S, Dressman JB, Amidon GL, Junginger HE, Midha KK, Barends DM. Biowaiver monographs for immediate release solid oral dosage forms: cimetidine. J Pharm Sci. 2006; 95: 974-84
	Fu = 0.81; Vss =1.00 L/kg; CLpo = 34.86 L/h	UWDIDB
	Caco-2 permeability = 3.6 10E-06 cm/s	Gnoth MJ, Buetehorn U, Muenster U, Schwarz T, Sandmann S. In vitro and in vivo Pglycoprotein transport characteristics of rivaroxaban. J Pharmacol Exp Ther. 2011; 338: 372-80
	CYP3A4 Ki = 23.0 □M	Haehner T, Refaie MO, Müller-Enoch D. Drug-drug interactions evaluated by a highly active reconstituted native human cytochrome P4503A4 and human NADPH-cytochrome P450 reductase system. Arzneimittelforschung. 2004;54(1):78-83.

UWDIDB: University of Washington Metabolism and Transport Database; parameter names are specific for SimCYP software.

Appendix Table 5. Input parameter for efavirenz

PhysChem and Blood Binding	
Mol Weight (g/mol)	315.67
log P	5.4

Compound Type	Monoprotic Base
pKa 1	10.2
B/P ratio	0.74
fu	0.029
Absorption	
fu(Gut)	1
Q(Gut) (L/h) predicted	9.174
Predicted Peff,man (10-4 cm/s)	1
Permeability Caco-2(10^{-06} cm/s)	8.920
Reference Compound	
Reference Compound Propranolol: 10^{-06} cm/s	21.15
Distribution	Full PBPK Model
Elimination	Recombinant system
fu mic	0.3
CYP3A4	
Vmax (pmol/min/pmol)	0.16
Km (□M)	23.5
CYP3A5	
Vmax (pmol/min/pmol)	0.6
Km (□M)	19.1
CYP1A2	CYP1A2
Vmax (pmol/min/pmol)	0.6
Km (□M)	8.3
CYP2B6	
Vmax	3.5
Km	6.4
CYP2A6	
Vmax (pmol/min/pmol)	1.08
Km (□M)	14.7
UGT2B7	
Vmax (pmol/min/pmol)	1.5
Km (□M)	16.1
CYPs Interaction	
CYP2B6	
Maximal induction: Ind max	5.76
CV (%)	13.7
MIA (pmol/mg microsomal protein)	247.164
Concentration causing 50% maximal induction: Ind C50 (μM)	0.82
CV (%)	71.9
Unbound fraction in incubation (fu inc)	1

Hill coefficient γ	1
CYP3A4	
Ind max	6.45
CV (%)	18.6
MIA (pmol/mg microsomal protein)	2043.617
Ind C50 (μM)	3.930
CV (%)	52.500
fu inc	1
γ	1

Appendix Table 6. Observed and PBPK model predicted naloxegol exposure ratio in the absence and in the presence of enzyme modulators. Naloxegol was given as a single oral dose of 25 mg (geometric means with 90% confidence interval)

Source: Tables 6-9, reference [1]. Ki values of 0.5, 3.5 and 84.5 μM from ketoconazole, diltiazem and rifampin, respectively.

	AUC Ratio		Cmax Ratio	
	Observed	**Simulated**	**Observed**	**Simulated**
Ketoconazole 400 mg q.d. for 5 days, naloxegol on day 4	12.85 (11.3,14.6)	13.14 (11.9,14.5)	9.58 (8.1,11.3)	7.75 (6.9, 8.6)
Diltiazem XR 240 mg q.d. for 5 days, naloxegol on day 4	3.41 (3.16,3.68)	2.80 (2.64,2.98)	2.85 (2.59,3.14)	2.28 (2.18,2.39)
Rifampin 600 mg q.d. for 10 days, naloxegol on day 10	0.11 (0.095,12.5)	0.24 (0.22,0.26)	0.25 (0.19,0.31)	0.27 (0.25,0.30)
Quinidine Single dose 600 mg co-administered with naloxegol	1.39 (1.31,1.46)	1.23 (1.21,1.25)	2.47 (2.19,2.78)	1.87 (1.81,1.93)

Appendix Table 7. Model predictions of naloxegol AUC and Cmax ratios when co-administered with moderate/weak CYP3A inhibitors using either minimal model [1] or full PBPK model [3] (geometric means with 90% confidence interval)

		Minimal PBPK model		Full PBPK model	
Inhibitor	**Dosing Regimens**	**AUC ratio (95% CI)**	**C_{max} ratio (95% CI)**	**AUC ratio (95% CI)**	**C_{max} ratio (95% CI)**
Fluconazole	200 mg qd for 5 days	2.81 (2.71~2.92)	2.4 (2.3~2.51)	1.83 (1.65~2.01)	1.52 (1.40~1.65)
Verapamil	120 mg tid for 5 days	2.21 (2.00~2.46)	1.97 (1.8~2.15)	2.53 (1.97~3.26)	2.36 (2.02~2.2.76)
Erythromycin	250 mg q6h for 5 days	3.47 (3.16~3.81)	2.77 (2.55~3.01)	3.36 (2.71~4.16)	2.30 (1.96~2.69)
	400 mg q6h for 5 days	4.63 (4.18~5.13)	3.42 (3.12~3.75)	4.46 (3.55~5.60)	2.73 (2.27~3.28)
Ciprofloxacin	500 mg bid for 5 days	1.01	1.02	1.01	1.02
Alprazolam	0.5 mg tid for single day	1.00	1.00	1.00	1.00
Amlodipine	10 mg qd for 2 weeks	1.22 (1.20~1.24)	1.20 (1.18~1.21)	1.16 (1.12~1.21)	1.12 (1.09~1.14)
Atorvastatin	80 mg qd for 5 days	1.08 (1.08~1.09)	1.13 (1.12~1.14)	1.04 (1.03~1.05)	1.08 (1.07~1.09)
Fluoxetine	80 mg qd for 5 days	1.26 (1.23~1.29)	1.22 (1.20~1.24)	1.22 (1.15~1.30)	1.14 (1.11~1.18)
Cimetidine	800 mg qd for 5 days	1.35 (1.33~1.37)	1.31 (1.30~1.33)	1.28 (1.25~1.31)	1.22 (1.19~1.25)

Source: Table 2 reference [3].

Appendix Table 8. Model predictions of naloxegol AUC and Cmax ratios when co-administered with different CYP3A modulators using either minimal model [1] or full PBPK model [3]

	AUC ratio (90% CI)		
Inhibitor	Observed	Minimal PBPK model	Full PBPK model
Ketoconazole DDI	12.85 (11.3, 14.6)	13.14 (11.9, 14.5)	8.82 (7.17, 10.9)
Diltiazem DDI	3.41 (3.16, 3.68)	2.80 (2.64, 2.98)	2.45 (2.10, 2.86)
Rifampin DDI	0.11 (0.095, 0.125)	0.24 (0.22, 0.26)	0.37 (0.31,0.43)

Source: Table 1 reference [3]. P-gp inhibition Ki values, required for the updated full model, were 0.1, 5, 11, and 7.5 μM for verapamil, erythromycin, amlodipine, and atorvastatin, respectively.

Appendix Table 9.

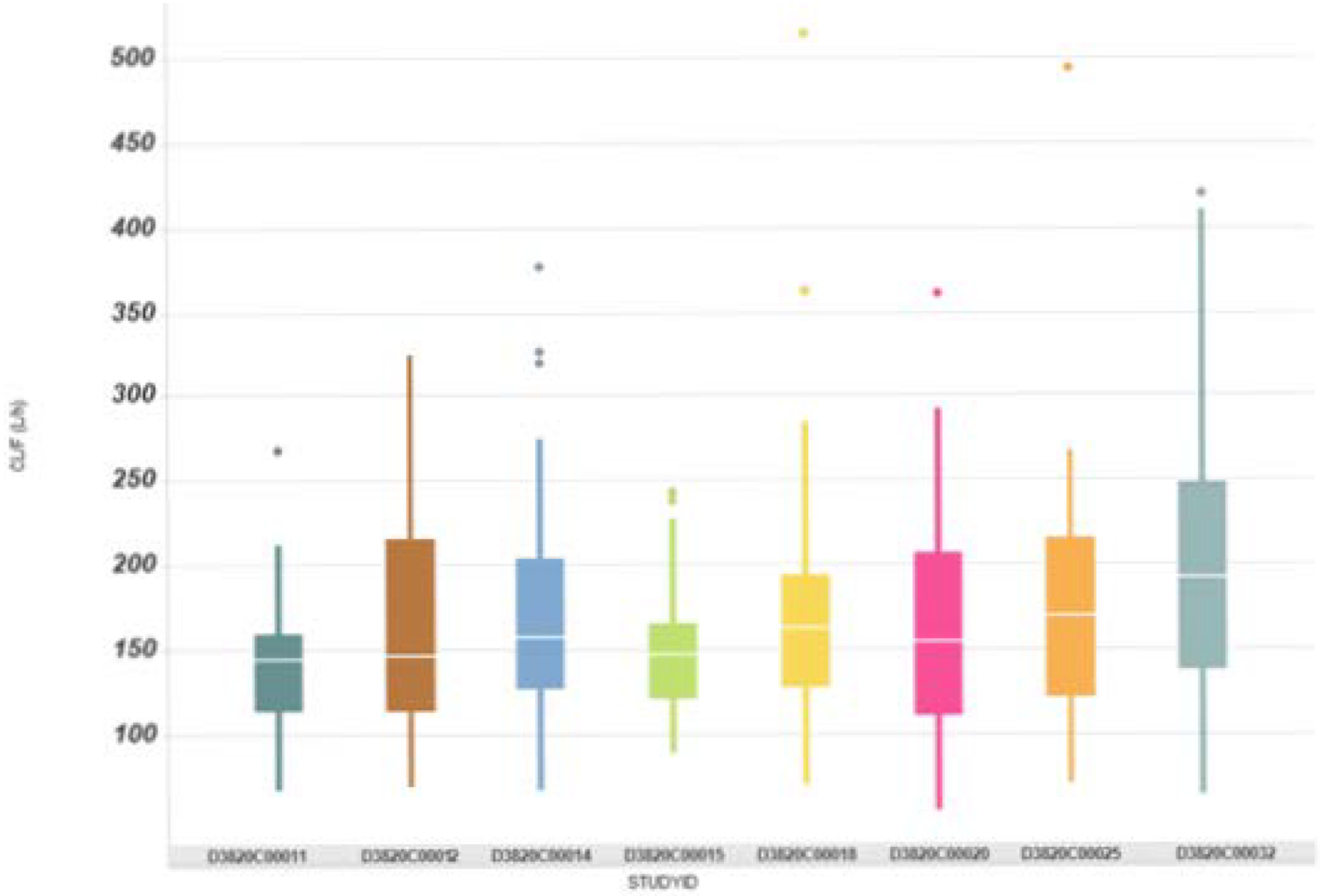
Table 20 Simulation results of PK parameters of naloxegol when co-administered with efavirenz, with and without induction of intestinal CYP3A4 (geometric means with 95% or 90% CI)

	Naloxegol	**Naloxegol plus efavirenz; with induction of intestinal CYP3A4**	**Naloxegol plus efavirenz; without induction of intestinal CYP3A4** [a]
AUC_{0-24} (95% CI)	130 (110~154)	63.8 (54.2~75.0)	97.7 (83.2~115)
C_{max} (95% CI)	26.2 (22.3~30.6)	13.5 (11.5~15.7)	20.6 (17.6~24.0)
AUC ratio (95% CI)	NA	0.49 (0.46~0.52)	0.75 (0.72~0.78)
C_{max} ratio (95% CI)	NA	0.51(0.48~0.55)	0.78 (0.76~0.81)

Modified from Table 1 of reference [4]. Design: administration of a single dose of naloxegol 25 mg on Day 14 of a 14-day dosing regimen with efavirenz 400 mg a.d.

CI Confidence interval. [a] *Sponsor provided an alternative model of naloxegol for this simulation. The model contains an additional pathway arbitrarily assigned to CYP2J2. It is not clear how this alteration results in decreased effect of intestinal CYP3A induction on naloxegol PK, however, the original naloxegol simulation represents a worst case scenario to support the use of 25 mg naloxegol when a moderate CYP3A inducer is co-administered.*

Appendix Figure 1. Box plot of CL/F values in clinical pharmacology studies using Phase III tablet formulation (data from the renal and hepatic impairment studies were not included).
Source: Figure 1 reference [3]



References

1. ASTRAZENECA PHARMACEUTICALS LP. Naloxegol (NDA-204760) study report: Physiologically Based Pharmacokinetic Modeling using SimCYP (version 12) to evaluate the Systemic Exposure of Naloxegol in the Presence of CYP3A Inhibitors. June 28 2013.
2. ASTRAZENECA PHARMACEUTICALS LP. Naloxegol (NDA-204760) study report: Summary of Clinical Pharmacology Studies, Naloxegol (formerly known as NKTR-118) for the Treatment of Opioid Induced Constipation (OIC). June 31 2013.
3. ASTRAZENECA PHARMACEUTICALS LP. Response to 25 October 2013 information request from the United States Food and Drug Administration (FDA) regarding review of the Naloxegol PBPK report Naloxegol (formerly known as NKTR-118) for the treatment of opioid induced constipation (OIC). 11 November 2013 (Email).
4. ASTRAZENECA PHARMACEUTICALS LP. Response to 29 April 2014 information request from the United States Food and Drug Administration (FDA) regarding Naloxegol PBPK modeling Naloxegol (formerly known as NKTR-118) for the treatment of opioid-induced constipation (OIC). 1 May 2014.
5. SimCYP manual: A Guide for IVIVE and PBPK/PD Modeling using the SimCYP Population-based Simulator version 12, CERTARA™ 2013.
6. Jamei M, Marciniak S, Feng K, Barnett A, Tucker G, Rostami-Hodjegan A. The SimCYP((R)) Population-based ADME Simulator. Expert Opin Drug Metab Toxicol 2009;5(2):211-23.
7. Horie K, Tang F, Borchardt RT. Isolation and characterization of Caco-2 subclones expressing high levels of multidrug resistance protein efflux transporter. Pharm Res. 2003; 20:161-8
8. Neuhoff S , Yeo KR, Barter Z, Jamei M, Turner DB, Rostami-Hodjegan A. Application of permeability-limited physiologically-based pharmacokinetic models: part II - prediction of PGlycoprotein mediated drug–drug interactions with digoxin. J Pharm Sci 2013;102(9);3161-3173.
9. Rodgers T, Rowland M. Physiologically based pharmacokinetic modelling 2: predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions. J Pharm Sci. 2006 95:1238-57.
10. Rodgers T, Leahy D, Rowland M. Physiologically based pharmacokinetic modeling 1: predicting the tissue distribution of moderate-to-strong bases. J Pharm Sci. 2005 94:1259-7.
11. Rekić D, Röshammar D, Mukonzo J, Ashton M. In silico prediction of efavirenz and rifampicin drug-drug interaction considering weight and CYP2B6 phenotype. Br J Clin Pharmacol. 2011:71(4):536-543.
12. Rabel SR, Maurin MB, Rowe SM, Hussain M. Determination of the pKa and pH-solubility behavior of an ionizable cyclic carbamate, (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one (DMP 266). Pharm Dev Technol. 1996;1:91-5.
13. Shou M, Hayashi M, Pan Y, Xu Y, Morrissey K, Xu L, Skiles GL. Modeling, prediction, and in vitro in vivo correlation of CYP3A4 induction. Drug Metab Dispos. 2008;36:2355-70.
14. Kalvass JC, Polli JW, Bourdet DL, Feng B, Huang S-M, Liu X, et al. Why clinical modulation of efflux transport at the human blood–brain barrier is unlikely: the ITC evidence based position. Clin Pharmacol Ther. 2013;94(1):80-94.
15. Xu Y, Zhou YH, Hayashi M, Shou M, Skiles G. Simulation of Clinical Drug-Drug Interactions from Hepatocyte CYP3A4 Induction Data and Its Potential Utility in Trial Designs. DMD 39:1139–1148, 2011.
16. FDA NDA 205552 ibrutinib Clinical Pharmacology Review 11/13/2013. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**204760**	**Brand Name**	**TBD**
OCP Division (I, II, III, IV, V)	**DCP III**	**Generic Name**	**Naloxegol Oxalate**
Medical Division	**DGIEP**	**Drug Class**	**Peripherally Acting mu-opioid receptor antagonists (PAMORA)**
OCP Reviewers	**Sandhya Apparaju, Ph.D. Elizabeth Shang, Ph.D.**	**Indication(s)**	**Treatment of Opioid-induced Constipation (OIC) in adults with chronic non-cancer pain**
OCP Team Leader	**Sue Chih Lee, Ph.D.**	**Dosage Form**	**Film coated Tablets (IR)**
Pharmacometrics Reviewer Pharmacometrics signatory/TQT review PBPK Team Leader	**Dr. Justin Earp Dr. Kevin Krudys Dr. Ping Zhao**	**Dosing Regimen**	**25 mg once daily**
Date of Submission	**September 16, 2013**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**05/16/2013**	**Sponsor**	**AstraZeneca Pharmaceuticals LP**
Medical Division Due Date	**07/16/2013**	**Priority Classification**	**Standard**
PDUFA Due Date	**09/16/2013**		

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**	**51 (Total)**		**13 phase 1 1 TQT 1 Phase 2 2 PBPK 3 population PK/E-R 5 *in vivo* metabolic profiling 10 bioanalytical reports 12 *in vitro* studies 5 phase 3**
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	10	**10**	
I. Clinical Pharmacology				
Mass balance:	**X**	2	**2**	^{14}C-labeled drug; MB study; metabolite profiling report
Isozyme characterization:	**X**			
Blood/plasma ratio:	**X**			
Plasma protein binding:	**X**			
Pharmacokinetics (e.g., Phase I) -	**X**			
Healthy Volunteers-				
single dose:	**X**	1	**1**	PK and PD
multiple dose:	**X**	2	**2**	Caucasians, Japanese
Patients-				
single dose:				
multiple dose:	**X**			
Dose proportionality -				

fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	4	**4**	In vivo studies with Quinidine, ketoconazole, rifampin, diltiazem
In-vivo effects of primary drug:				
In-vitro:	**X**	12	**12**	In vitro ADME, DDI studies
Subpopulation studies -				
ethnicity:	**X**	5	**3**	5 phase 3 studies; pop PK covariate
gender:	**X**			pop PK covariate
pediatrics:				
geriatrics:	**X**			pop PK covariate; PK in elderly also evaluated as part of Japanese PK study
renal impairment:	**X**	1	**1**	PK and safety in Control *vs.* Moderate, Severe, ESRD RI
hepatic impairment:	**X**	1	**1**	PK and safety in control vs. HI (severe not studied)
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	2	**2**	Phase 1 PK/PD; TQT study
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**X**	1	**1**	Phase II and Phase III trials
II. Biopharmaceutics	**X**	3	**2**	BA/BE, food effect studies
Absolute bioavailability				
Relative bioavailability -				
solution as reference:	**X**	1		
alternate formulation as reference:	**X**	1		
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	1		Clinical vs. To-be-marketed; ONDQA Biopharm will review report, OSI inspection & analytical assays
replicate design; single / multi dose:				
Food-drug interaction studies	**X**			Food effect evaluated as part of BA/BE studies; pivotal BE and Japanese PK study
Bio-waiver request based on BCS				
BCS class				Proposed to be a Class III drug
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies	X	5	6	2 PBPK reports; 4 metabolite profiling reports
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**X**			
Literature References	**X**			
Total Number of Studies	**X**	**51**	**47**	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			

3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	NA			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDHYA K APPARAJU
05/14/2014

ELIZABETH Y SHANG
05/14/2014

JUSTIN C EARP
05/14/2014

NITIN MEHROTRA
05/14/2014

YUZHUO PAN
05/14/2014

PING ZHAO
05/14/2014

SUE CHIH H LEE
05/14/2014

HAE YOUNG AHN
05/14/2014

Part 2: Clinical Pharmacology and Biopharmaceutics- Individual Study Reviews

for

NDA 204760- Naloxegol for Opioid Induced Constipation (OIC) in Chronic Non-Cancer Pain Patients

APPEARS THIS WAY ON ORIGINAL

D3820C00012: An Open-label, 1-sequence, 3-period, 3-treatment, Crossover Study to Assess the Effects of Ketoconazole on the Pharmacokinetics of NKTR-118 in Healthy Subjects

Background: In vitro data indicate that NKTR-118 is metabolized by CYP3A4 and is a substrate of p-glycoprotein (Pgp). The primary objective of the study was to investigate the effect of ketoconazole, a strong CYP3A4/P-gp inhibitor on the PK of NKTR-118 in healthy volunteers. The PK parameters evaluated included Cmax, tmax, AUC(0-t), AUC(0-24), AUC, λz, t1/2,λz, CL/F, Vz/F. Secondary objectives are that of safety and tolerability of drug alone and in combination with ketoconazole. Adverse events, laboratory assessments (clinical chemistry, hematology, and urinalysis), physical examination, 12-lead ECG, vital signs, C-SSRS were assessed.

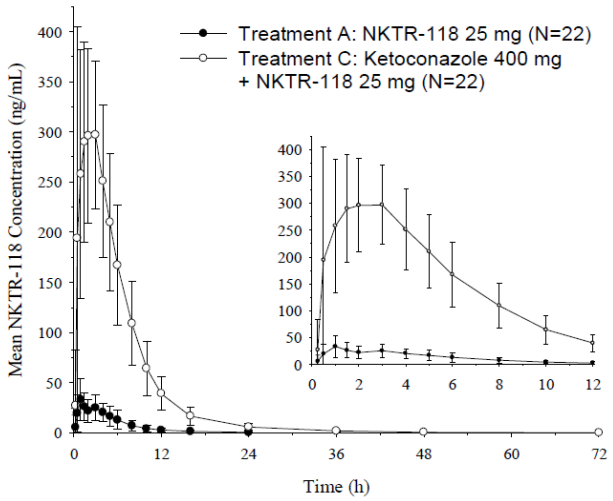
Design: An open-label, non-randomized, fixed-sequence study in healthy men and women between 18-55 years inclusive. N = 22 were enrolled and included in safety and PK analyses. There were 21 males, and one female; 13 were blacks and 9 whites; Mean age was 34 years. Following a screening period, volunteers received a single oral dose of 25 mg naloxegol (film coated tablet) on day 1 (Treatment A), followed by a 2-day washout. Volunteers then received oral doses of 400 mg ketoconazole once daily on the mornings of days 4 to 8 (5 days) (Treatment B); on day 7, 25 mg naloxegol was coadministered with ketoconazole (Treatment C). Drug was administered in the morning under fasted condition. A meal was allowed 4 hours after dosing on Days 1 and 7. Serial blood samples for naloxegol determination in plasma were collected for 72 hours after dosing on days 1 and 7 [predose (within 30 minutes prior to dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours post-dose].

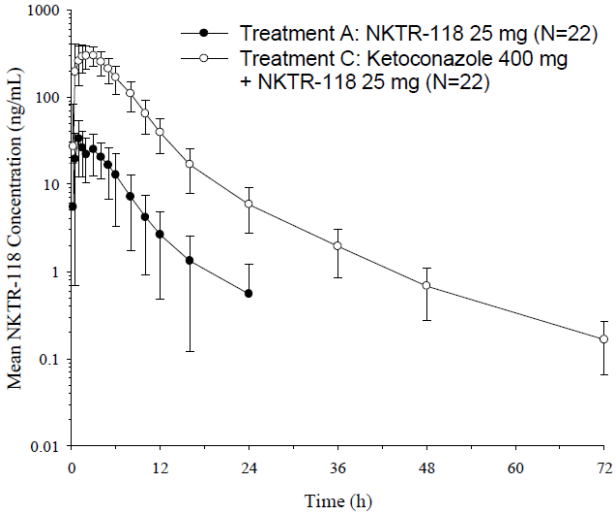
Statistical analyses employed by sponsor: The effect of ketoconazole 400 mg was assessed using an analysis of variance model for the primary PK parameters AUC and Cmax, on log scale. Treatment was included as a fixed effect and volunteer was included as a random effect in the model. Geometric least-squares (LS) means by treatment, and geometric LS mean ratios, i.e., NKTR-118 plus ketoconazole (Treatment C) versus NKTR-118 alone (Treatment A), together with 2-sided 90% confidence intervals (CIs) were presented for AUC and Cmax. *If the 90% CIs for the ratios were completely contained within the pre-specified limits (70% to 143%) then lack of PK impact of ketoconazole on NKTR-118 was to be concluded.* Secondary PK parameters AUC(0-t) and AUC(0-24) for Treatments A and C were also assessed in a similar fashion.

Sponsor notes also that "The sample size justification noted above does not utilize the conventional 0.8 to 1.25 range used to establish equivalence, rather, a wider interval was used because some level of interaction between NKTR-118 and ketoconazole was expected and as such the study was designed to investigate the magnitude of the effect of ketoconazole on the PK of NKTR-118 rather than to formally establish equivalence".

Results:

Arithmetic mean concentrations versus time plots for treatment A (drug alone) and treatment C (drug with ketoconazole) are shown below; data indicate a dramatic increase in plasma concentrations following co-administration of naloxegol (NKTR-118) with ketoconazole (on the fourth day of 400 mg qd regimen). All individuals showed consistent increase in exposure with ketoconazole, and secondary peaks were noted for most subjects in the drug alone as well as the co-administration treatments.





A summary of the A. Mean pharmacokinetic parameters is provided below; Data support substantial and clinically important changes in systemic PK following co-administration of naloxegol with ketoconazole:

Arithmetic mean ± S.D. (% CV)	Naloxegol 25 mg alone (Trt A) (n = 22)	Naloxegol + Ketoconazole (Trt C) (n =22)
Tmax (h); Median (range)	1.00 (0.25 – 5.00)	1.50 (0.5 - 3.00)
Cmax (ng/mL)	43 ± 18.6 (47 %)	392 ± 119 (30 %)
AUC0-24 (ng h/mL)	174 ± 70 (42 %)	2140 ± 540 (25 %)
AUC0-t (ng h/mL)	178 ± 74 (43 %)	2210 ± 569 (26 %)
T1/2 (h)	7.6 ± 6.2 (57 %)	9.5 ± 2.2 (25 %)
Vz/F (L)	1550 ± 822 (53 %)	164 ± 60 (35 %)
CL/F (L/h)	163 ± 68 (44 %)	12 ± 3 (26 %)

On average, 9-fold and 12.5 fold increases were noted in Cmax and AUC0-t when naloxegol was co-administered with ketoconazole. A significant decrease in apparent clearance by ~ 13-fold was noted with ketoconazole coadministration, while the volume of distribution decreased by ~ 9.5 fold on average. The differences in Tmax and T1/2 were not marked compared to other PK parameters.

The inter- and intra-subject variability for various PK parameters is summarized and appeared to be low to moderate:

	Source of Variability			
	Inter-subject		Intra-subject	
Parameter (units)	CV%	90% Confidence Interval	CV%	90% Confidence Interval
AUC (ng*h/mL)	24.3	(17.4, 42.9)	25.1	(20.0, 34.2)
AUC(0-t) (ng*h/mL)	24.4	(17.4, 42.7)	24.9	(19.8, 33.9)
AUC(0-24) (ng*h/mL)	24.1	(17.3, 41.3)	23.7	(18.9, 32.3)
Cmax (ng/mL)	19.4	(11.7, 68.8)	33.2	(26.4, 45.7)

Statistical analyses using geometric mean data are presented below; the pre-specified bounds for bioequivalence were not the standard criteria, instead 70-143 % bounds was used for sample size calculation as the sponsor anticipated significant change with ketoconazole co-administration:

N = 22	**Treatment**	**Geometric LS mean**	**Ratio % (C/A)**	**90 % CI**
Cmax (ng/mL)	Naloxegol (A)	39.23	957.67	809.6 – 1132.8
	With Keto (C)	375.7		
AUC0-24 **(ng.h/mL)**	Naloxegol (A)	161.2	1289.44	1141.9 – 1456
	With Keto (C)	2079		
AUC0-t **(ng.h/mL)**	Naloxegol (A)	164.5	1300.07	1144.8–1476.4
	With Keto (C)	2138		
AUCinf **(n h/mL)**	Naloxegol (A)	166.8	1285.44	1130.6–1461.4
	With Keto (C)	2144		

The fold increases for Cmax, AUC0-t and AUCinf in presence of ketoconazole were 9.58, 13.00 and 12.85 fold, respectively. For all parameters, the mean ratios and 90 % CI intervals were completely outside the pre-specified bioequivalence range.

The significant increase in Cmax and AUC parameters as well as the decreased clearance in presence of ketoconazole suggests impairment of systemic CYP3A4 mediated metabolism of naloxegol. The increase in exposure could also be due to inhibition of gut CYP3A4, and P-gp efflux transporter thus increasing intestinal absorption and overall bioavailability when co-administered with ketoconazole.

Safety and tolerability of these high exposures of naloxegol are of interest, as in the prior studies including a phase 2 dose-ranging study, dose-limiting side effects such as abdominal pain and diarrhea have been reported at doses only twice that of the clinically proposed dose of 25 mg qd. However, no marked differences in safety as noted by

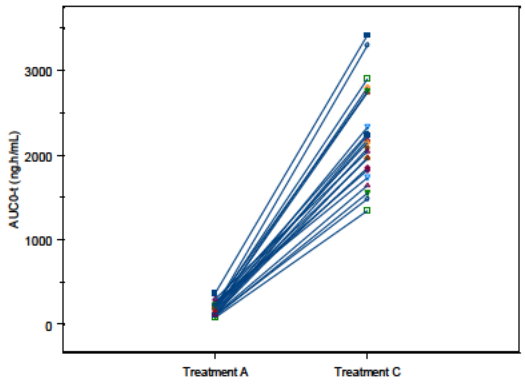
adverse events and severity were noted in this single dose PK study. The following is a summary of the safety events noted in this DDI study:

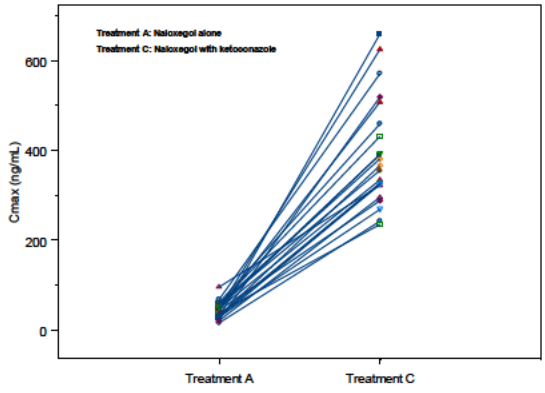
There were no deaths, SAEs, or AEs leading to study discontinuation. Overall, 10 (45.5%) volunteers experienced at least 1 AE during the study: 4 (18.2%) volunteers had AEs during NKTR-118 alone (Treatment A), 3 (13.6%) volunteers had AEs during ketoconazole alone (Treatment B), and 6 (27.3%) volunteers had AEs during the combination therapy (Treatment C). There were no AEs of severe intensity and no other significant AEs during the study. Thus the numbers of volunteers with AEs was slightly higher during the combination treatment (Treatment C) than during the NKTR-118 or ketoconazole alone treatments (Treatments A and B, respectively).

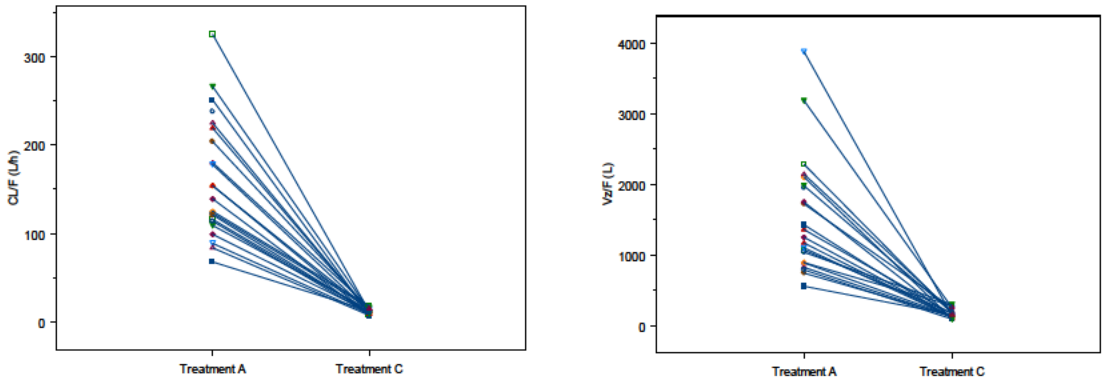
	Number (%) of subjects			
System organ class/ Preferred term	**Treatment A N=22**	**Treatment B N=22**	**Treatment C N=22**	**Overall N=22**
Subjects with any AE	4 (18.2%)	3 (13.6%)	6 (27.3%)	10 (45.5%)
Gastrointestinal disorders	2 (9.1%)	0	2 (9.1%)	4 (18.2%)
Abdominal pain	1 (4.5%)	0	1 (4.5%)	2 (9.1%)
Nausea	1 (4.5%)	0	1 (4.5%)	2 (9.1%)
Vomiting	0	0	1 (4.5%)	1 (4.5%)
General disorders and administration site conditions	1 (4.5%)	0	3 (13.6%)	3 (13.6%)
Asthenia	0	0	1 (4.5%)	1 (4.5%)

Sponsor also notes that there were no trends or clinically meaningful changes noted in mean or median vital signs throughout the study. There were no AEs reported for abnormal vital signs and individual vital signs remained generally stable. There were no AEs for abnormal ECG findings and no ECGs were assessed by the Investigator as abnormal and clinically significant.

Reviewer's analysis:



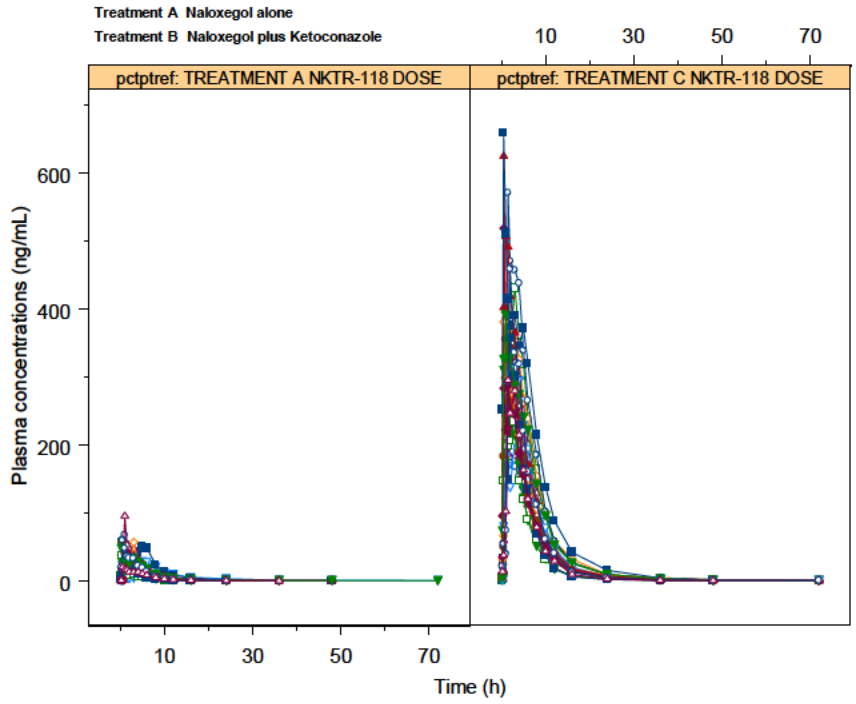


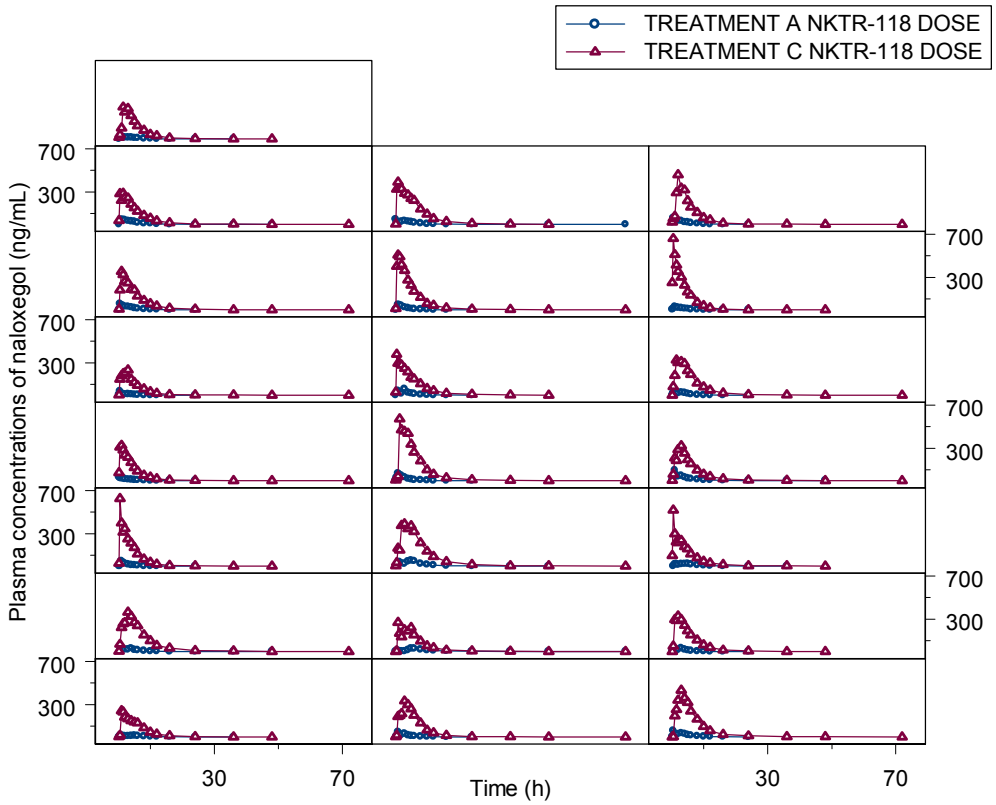


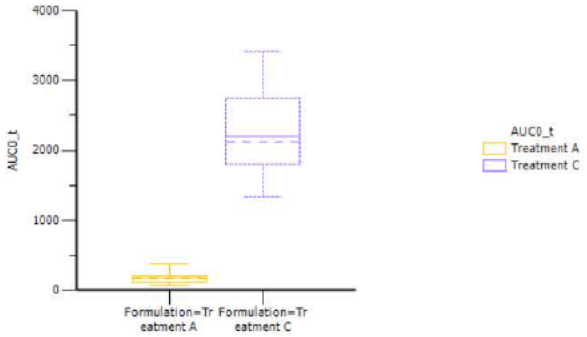
Treatment A: Naloxegol; Treatment B: Naloxegol with Ketoconazole

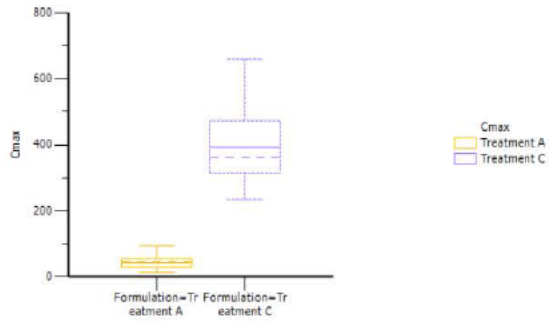
Dependent	FormRef	TestGeoLSM	Ratio__Ref_	CI-90_Lower	CI_90_Upper
Ln(AUC0_t)	Treatment A	2137.9989	1300.0697	1092.3124	1547.3424
Ln(AUCinf)	Treatment A	2143.5348	1285.4414	1079.3279	1530.9154
Ln(Cmax)	Treatment A	375.70186	957.67049	791.22665	1159.1277

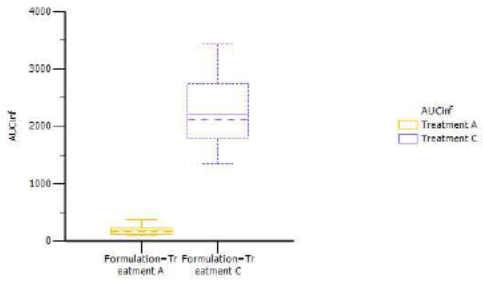
Sponsor proposes to contraindicate use of Strong CYP3A4 inhibitors with naloxegol; this is reasonable given the markedly higher exposures noted in presence of ketoconazole;




TREATMENT A NKTR-118 DOSE
TREATMENT C NKTR-118 DOSE
Plasma concentrations of naloxegol (ng/mL)
700
300
30
70
Time (h)





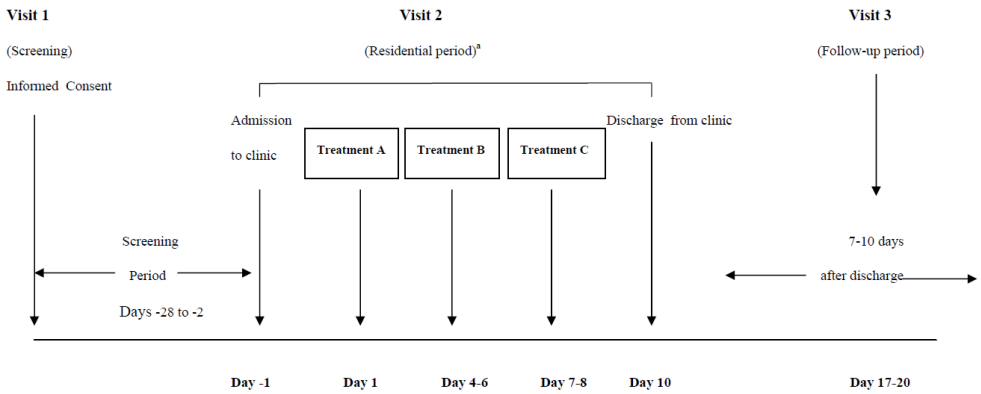


D3820C00032- An Open-label, sequential, 3-period study to assess the Effects of Diltiazem on the Pharmacokinetics of Naloxegol in Healthy Subjects

Design: This was an open-label, non-randomized, fixed-sequence study to assess the effect of diltiazem XR on the PK of naloxegol in healthy volunteers (n = 43).

Following a screening period of up to 28 days, volunteers reported to the study center on Day -1 for admission and assessment of continued eligibility. A single dose of 25 mg naloxegol was administered on Day 1 (Treatment A) followed by a 2-day washout (Days 2 and 3). Once-daily doses of 240-mg diltiazem XR were administered on Days 4 through 6 (Treatment B). Co-administration of 25 mg naloxegol with 240 mg diltiazem XR occurred on Day 7 with an additional dose of 240 mg diltiazem XR administered on Day 8 (Treatment C). Volunteers were required to fast from 10 hours before until 4 hours after investigational product (IP) administration on Day 1 and Day 7. Naloxegol PK samples were collected on Days 1 and 7 at predose (within 30 minutes prior to dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours following naloxegol administration.

Figure 1 **Flow chart of study design**



[a] **Treatment A**: Naloxegol 25 mg on Day 1 only (Note: Days 2 and 3 were the washout period from naloxegol)
Treatment B: Diltiazem XR 240 mg once daily on Days 4 to 6
Treatment C: Diltiazem XR 240 mg plus naloxegol 25 mg on Day 7 followed by 1 additional diltiazem XR 240-mg tablet on the morning of Day 8

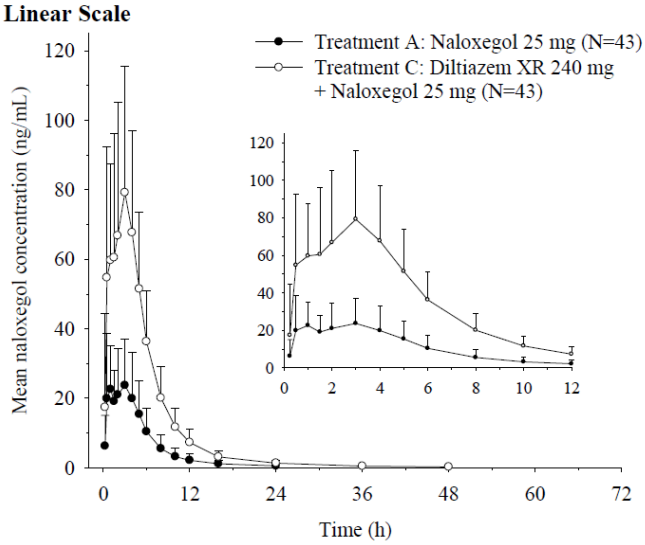
Rationale: Diltiazem is in a group of drugs called calcium channel blockers and is a moderate inhibitor of the CYP3A4 enzyme system. Coadministration of diltiazem and drugs primarily metabolized by the CYP3A4 enzyme system may result in increased plasma concentrations of the drugs that could increase or prolong both therapeutic and adverse effects. Naloxegol is metabolized by CYP3A4. Analysis of ^{14}C radioactivity indicated obvious levels of metabolites in the systemic circulation and in the excreta. Thus, CYP3A-mediated metabolism may play a major role in the clearance of naloxegol.

Study objectives and variables assessed were as follows:

Objective			Variable
Priority	**Type**	**Description**	**Description**
Primary	PK	To investigate the effect of coadministration of diltiazem on the PK of naloxegol in healthy volunteers	Primary variables: C_{max} and AUC Secondary variables: t_{max}, $t_{1/2\,\lambda z}$, λ_z, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}24)}$, CL/F, and V_z/F
Secondary	Safety	To assess the safety and tolerability of naloxegol when administered alone and in combination with diltiazem XR tablets	Adverse events, laboratory assessments (clinical chemistry, hematology, and urinalysis)[a], vital signs (blood pressure and pulse rate), 12-lead ECG, physical examination, and C-SSRS

Statistical analysis: The effect of diltiazem XR 240 mg on the PK of naloxegol 25 mg was assessed using an analysis of variance model for primary PK parameters (AUC and Cmax) and secondary parameters [AUC(0-t) and AUC(0-24)] on logarithmic scale. Treatment was included as a fixed effect and volunteer was included as a random effect in the model. Geometric least-squares (LS) means by treatment with 95% confidence intervals (CI), and geometric LS means ratios for the treatment effect of naloxegol plus diltiazem XR (Treatment C, test) versus naloxegol alone (Treatment A, reference) together with 90% CIs were presented for AUC and Cmax. If the 90% CIs for the ratios (for both AUC and Cmax) were found to be completely contained within the pre-specified limits (80%, 125%) then a lack of PK impact of diltiazem XR on naloxegol was to be concluded.

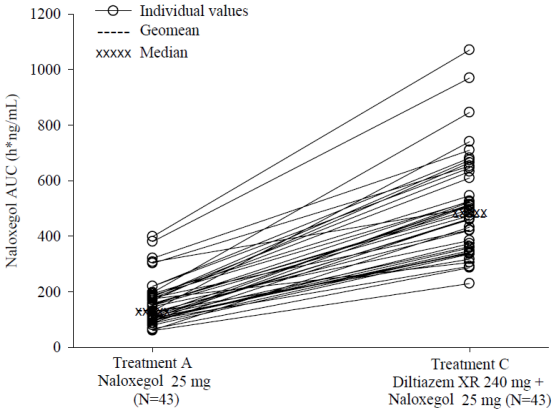
Results: The mean plasma concentration-time profiles for naloxegol with and without moderate CYP3A4 inhibitor drug Diltiazem are shown below; most profiles were bimodal and concentrations in presence of diltiazem were obviously greater at all the time points compared to naloxegol alone:

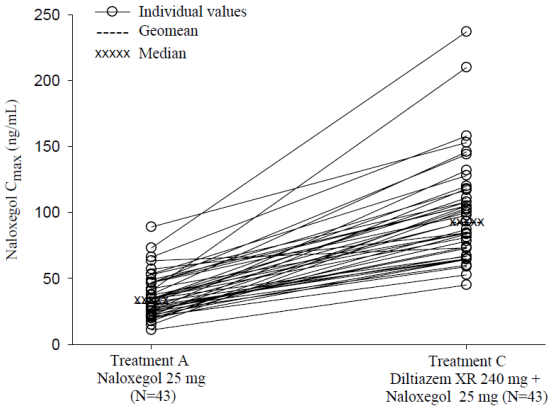


The naloxegol mean arithmetic PK parameters with and without diltiazem are shown below:

Arithmetic mean ± SD	Naloxegol alone (n = 43)	Naloxegol + Diltiazem (N= 43)
Cmax (ng/mL)	36 ± 16	100 ± 39
AUC0-t (ng h/mL)	154 ± 79	503 ± 182
AUC0-inf (ng.h/mL)	156 ± 81	506 ± 182
AUC0-24 (ng.h/mL)	150 ± 73	489 ± 174
Tmax (h)	1.0 [0.25 – 5.0]	3.0 [0.5- 5.0]
T1/2 (h)	6.72 ± 3.45	8.46 ± 2.49
CL/F (L/h)	197 ± 87	55 ± 19
Vz/F (L)	1730 ± 775	663 ± 289

Data suggests that in presence of a moderate CYP3A4 inhibitor drug Diltiazem, the Cmax and AUC of naloxegol increased markedly, while the clearance reduced suggesting inhibition of CYP3A4 mediated clearance of naloxegol. The Vz/F was decreased for naloxegol in the presence of diltiazem.





Statistical analysis: The 90 % CI ratios were well above the pre-specified no effect bounds suggesting a significant impact of diltiazem on naloxegol PK; Cmax and AUC of naloxegol increased by 2.86-fold and 3.41-fold, respectively in presence of diltiazem.

N = 43;	Ratio %	90 % CI
Cmax (ng/mL	285.74	(259.48 – 314.66)
AUC0-t (ng/h/mL)	344.28	(318.63 – 371.98)
AUC0-inf (ng.h/mL)	341.29	(316.00 – 368.60)

D3820C00011: A Randomized, 2-Part, Crossover, Single center Study to Evaluate Effect of Quinidine on the Pharmacokinetics of NKTR-118 and the Concomitant Effect of Quinidine and NKTR-118 on Morphine-induced Miosis

Study rationale: In vitro data indicate NKTR-118 is a substrate of P-glycoprotein (Pgp), and therefore it is desirable to study whether inhibitors of Pgp, which is an integral part of the BBB, may alter the reduced capacity of NKTR-118 to cross into the brain, where it could result in withdrawal of opioid-mediated pain relief and resultant withdrawal adverse effects.

Objectives: The primary objective was to investigate the effect of quinidine on the PK of NKTR-118 in healthy volunteers. Secondary objectives were to investigate the effect of coadministration of NKTR-118 and quinidine on morphine-induced miosis and to investigate the safety and tolerability of NKTR-118 when administered alone and in combination with morphine and/or quinidine.

Study design: a double-blind (with regard to quinidine administration), randomized, 2-part, crossover, single-center study in n = 38 male and female healthy volunteers between ages 18- 55 years inclusive.

The study consisted of 2 parts, each of which comprised 2 periods. In Part 1 on Day 1 of Period 1, volunteers received a single oral dose of NKTR-118 25 mg and quinidine placebo (Treatment A) or NKTR-118 25 mg and quinidine 600 mg (Treatment B). Following at least a 7-day washout period, volunteers received the alternate treatment on Day 1 of Period 2. The treatment sequences for Part 1 were AB or BA.

On Day 1 of Part 2, Period 3, a subset of volunteers returned to the clinic (at least 14) and were randomly assigned to receive either Treatment C (oral administration of NKTR-118 25 mg and quinidine placebo and intravenous administration of 5 mg/70 kg morphine) or Treatment D (oral administration of NKTR-118 25 mg and quinidine 600 mg and intravenous administration of 5 mg/70 kg morphine). Following at least a 7-day washout period, volunteers received the alternate treatment on Day 1 of Period 4. The treatment sequences for Part 2 were CD or DC.

NKTR-118 and quinidine were administered via oral route under fasted condition. Morphine was administered intravenously as a 1-minute slow injection. Both NKTR-118 and quinidine were orally dosed 15 minutes before morphine intravenous dose administration.

Thus the study treatment groups were as follows:
A: NKTR-118 25 mg and quinidine placebo;
B: NKTR-118 25 mg and quinidine 600 mg;
C: NKTR-118 25 mg, quinidine placebo and intravenous administration of 5 mg/70 kg morphine
D: NKTR-118 25 mg, quinidine 600 mg and intravenous administration of 5 mg/70 kg morphine

Blood sampling for PK: PK samples for the determination of NKTR-118 (naloxegol) were collected for 72 hours following the dose on day 1 of each treatment period in part 1; Plasma samples (NKTR-118) were collected at predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours postdose in both Treatments A and B. PK samples for the determination of morphine and naloxegol in plasma were collected for 24 hours following the dose on day 1 of each treatment period in part 2; plasma samples were collected prior to morphine dose and at 0.5, 1, 2, 4, 6, 8, and 24 hours following the morphine dose in both Treatments C and D. Samples were collected after the simultaneously scheduled pupillometry assessments. NKTR-118 was orally dosed 15 minutes before morphine intravenous dose administration, hence the scheduled postdose times for NKTR-118 relative to dose administrations were 0.75, 1.25, 2.25, 4.25, 6.25, 8.25, and 24.25 hours postdose.

PK and PD parameters assessed were as follows:

Part 1: NKTR-118 Cmax, tmax, t1/2λz, λz, AUC, AUC(0-t), AUC(0-24), CL/F, Vz/F
Part 2: NKTR-118, morphine, morphine-3-glucuronide, and morphine-6-glucuronide AUC, AUC(0-24), Cmax, and tmax

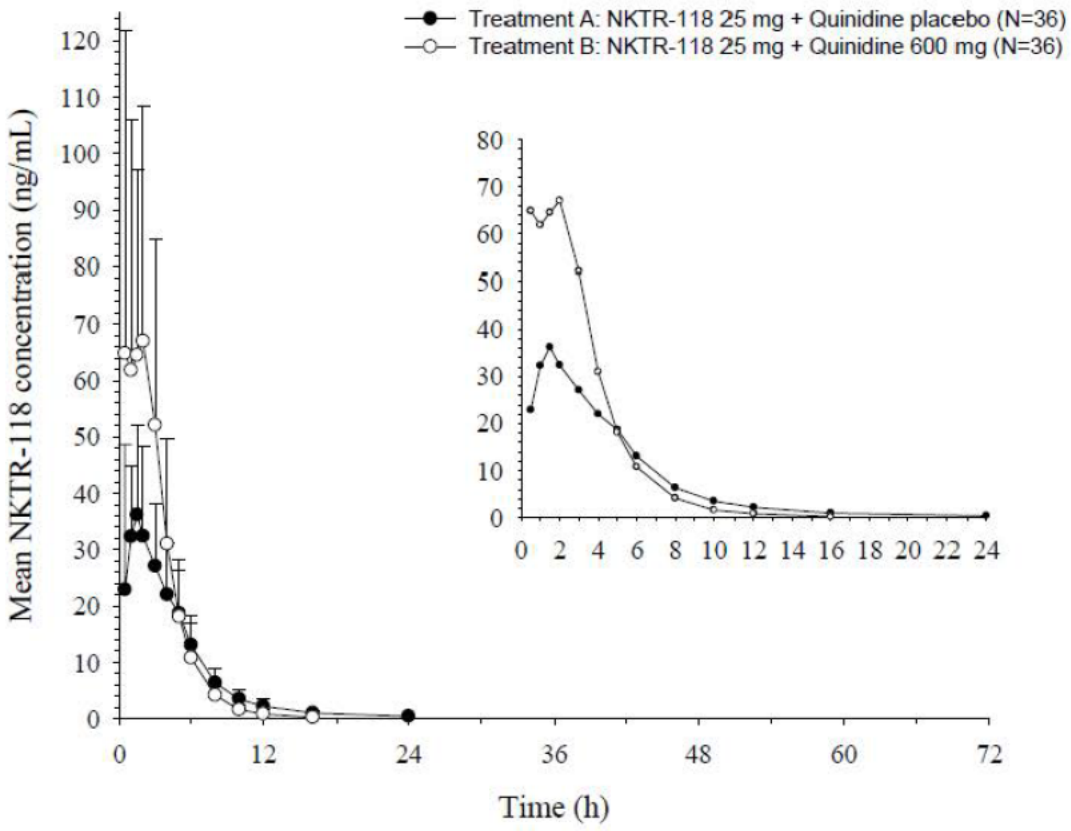
Part 2: Change from baseline in pupillary measurements on both eyes at each time point postdose measured in 4 different conditions: dark (after the volunteer had been dark adapted to the room for 5 minutes), 0.04 lux (scotopic), 0.4 lux (low mesopic), and 4.0 lux (high mesopic);
Overall pupil diameter was calculated by taking the mean of the assessments of the left and right eye. Overall peak miotic effect defined as the absolute value of the maximum, negative, overall pupil diameter change from baseline.

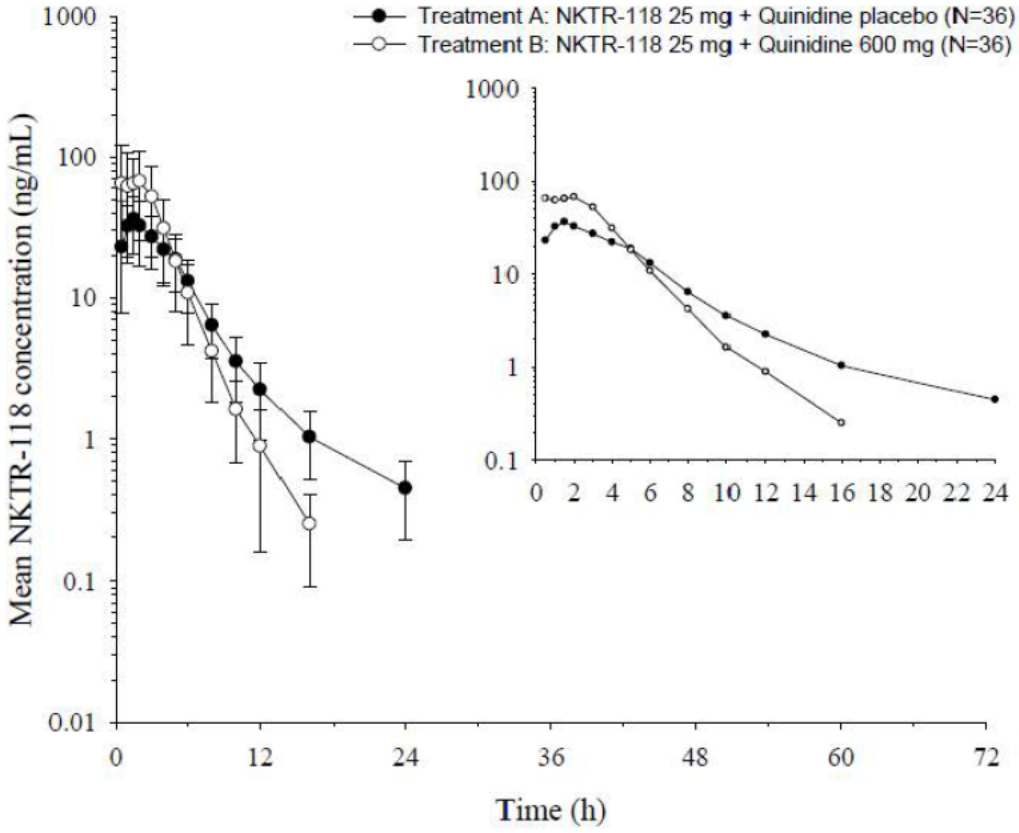
Safety assessments included adverse events, vital sign measurements, C-SSRS assessments, physical examinations, clinical laboratory tests (clinical chemistry, hematology, and urinalysis), ECG recordings, and telemetry

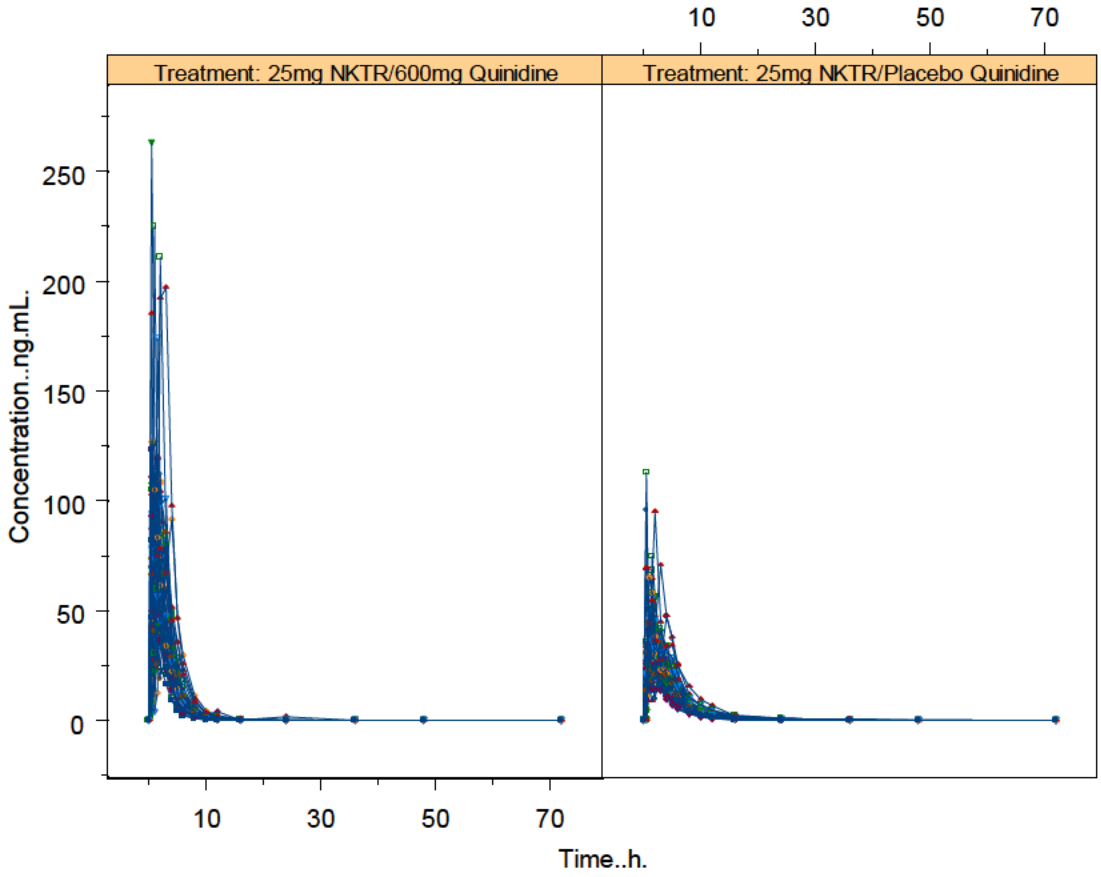
Statistical methods: A linear mixed-effect analysis of variance (ANOVA) model was used to compare the PK parameters AUC, Cmax, AUC(0-t), and AUC(0-24) on log scale. Treatment, period, and sequence were included as fixed effects and volunteer within sequence was included as a random effect in the model. The results of the analysis were presented in terms of geometric least-squares (LS) means by treatment, ratio of geometric LS means (NKTR-118 25 mg plus quinidine 600 mg versus NKTR-118 25 mg plus quinidine placebo) and 90% confidence interval (CI) for the ratio. If the 90% CI was completely contained within the limits (80% to 125%), a lack of effect of quinidine 600 mg on NKTR-118 25 mg PK was to be concluded.

Results: Study included 29 males and 9 females; mean age was 30; 24 subjects were White, 12 African American and 1 American Indian or Alaska Native. In part 2, 15 males and 4 females participated, with a mean age of 31 years; 15 were whites and 4 were AA. 36 subjects completed part 1 and 19 subjects completed part 2 of the study.

PK parameters: Arithmetic mean plasma-cocnentration time profiles of NKTR-118 with and without quinidine (a strong inhibitor of P-gp) are shown below; Coadminstration of quinidine resulted in higher mean naloxegol plasma concentrations initially, followed by rapid decline of naloxegol concentrations. Logarithmic mean profiles suggest that decline after 4 hours was rapid in the coadminstration group (B) compared to naloxegol alone (A).


Treatment A: NKTR-118 25 mg + Quinidine placebo (N=36)
Treatment B: NKTR-118 25 mg + Quinidine 600 mg (N=36)
Mean NKTR-118 concentration (ng/mL)
Time (h)


Treatment A: NKTR-118 25 mg + Quinidine placebo (N=36)
Treatment B: NKTR-118 25 mg + Quinidine 600 mg (N=36)
Mean NKTR-118 concentration (ng/mL)
Time (h)



Similar effect of quinidine on plasma NKTR-118 concentrations was also noted in the subset of patients who continued into the second (PD) component of this study. Plasma concentrations of NKTR-118 were also not affected when coadministered with morphine in the second part of the study. In addition during part 2, the exposure of morphine and its metabolites was not affected by the coadministration of quinidine.

Summary of PK parameters for naloxegol alone and with quinidine:

Arithmetic mean ± SD	**Naloxegol 25 mg alone (n = 36)**	**Naloxegol with Quinidine 600mg (n = 38)**
Cmax (ng/mL)	47 ± 21	114 ± 46
Tmax; Median [Range]	1.5 [0.5 – 4]	1.0 [0.5 – 3]
AUC0-24 (n.h/mL)	189 ± 59	327 ± 123
AUC0-t (ng h/mL)	191 ± 60	269 ± 93
AUCinf (ng h/mL)	194 ± 60	269 ± 95
CL/F	141 ± 42	102 ± 28
T1/2 (h)	7.2 ± 6.7	2.8 ± 1.6
Vz/F (L)	1460 ± 1414	406 ± 313

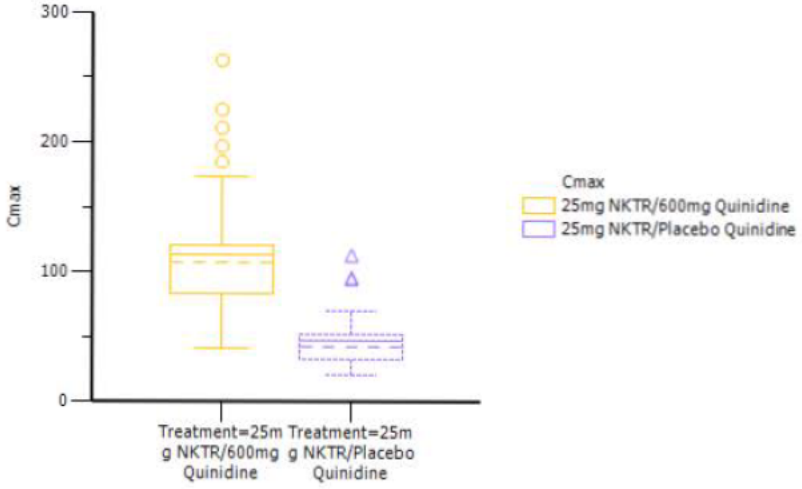
Statistical comparisons of treatments A (naloxegol alone) and B (naloxegol with Quinidine):

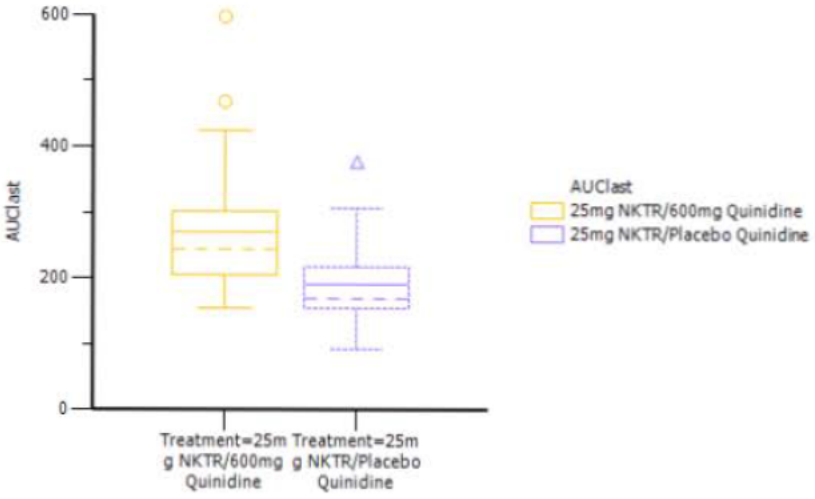
Part	Parameter	Trt [a]	n	Geometric LS mean	95% CI	Comparisons		
						Pair	Ratio (%)	90% CI
1	AUC	A	36	185.9	(168.2, 205.5)	B/A	138.72	(131.37, 146.48)
	(ng·h/mL)	B	34	257.9	(233.1, 285.3)			
	$AUC_{(0-t)}$	A	36	183.6	(166.2, 202.8)	B/A	141.29	(133.62, 149.39)
	(ng·h/mL)	B	36	259.4	(234.9, 286.5)			
	$AUC_{(0-24)}$	A	35	181.9	(163.8, 202.0)	B/A	163.17	(148.30, 179.53)
	(ng·h/mL)	B	12	296.8	(258.9, 340.1)			
	C_{max}	A	36	43.45	(38.26, 49.36)	B/A	246.61	(219.10, 277.57)
	(ng/mL)	B	36	107.2	(94.36, 121.7)			

Reviewer's bioequivalence analysis suggests similar data, in which all the treatment ratios and 90 % CI bounds for naloxegol PK parameters with and without quinidine were for the most part outside the standard bioequivalence 90 % CI bounds (i.e. 80- 125 %) suggesting statistically significant effect of co-administrated quinidine on naloxegol exposures.

Variable	Ratio (Test/Ref)	CI_90_Lower	CI_90_Upper
Ln(AUCinf)	138.08	122.53	155.61
Ln(AUClast)	140.34	124.82	157.78
Ln(Cmax)	244.28	210.23	283.84

Based on the statistical analyses of the geometric least square means for exposure parameters, there was a 2.4-fold increase in Cmax, and 1.4-fold increase in the AUC parameters of naloxegol in presence of 600 mg quinidine. Based on observation of the mean PK parameters for the two treatments, half-life of NKTR-118 reduced on average by 4.4 h in presence of quinidine, while Vz/F reduced by >3-fold. Median Tmax occurred somewhat earlier in presence of quinidine. CL/F was reduced but modestly (~ 28 %).

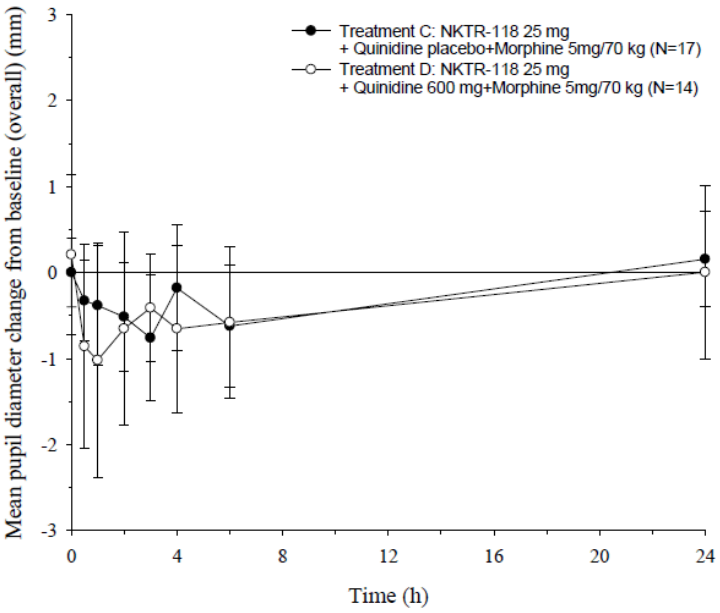

300
200
100
0
Cmax
Treatment=25mg NKTR/600mg Quinidine
Treatment=25mg NKTR/Placebo Quinidine
Cmax
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine


600
400
200
0
AUClast
Treatment=25mg NKTR/600mg Quinidine
Treatment=25mg NKTR/Placebo Quinidine
AUClast
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine

Pharmacodynamics: Impact of quinidine co-administration on morphine-induced miosis was evaluated in part 2 of this study to rule out potential increased uptake of NKTR-118 into the brain due to inhibition of P-gp efflux transporter. Miosis, or constriction of the pupil produced by morphine is a surrogate for the central effect of morphine.
Treatments in part 2 are as follows:
C: NKTR-118 25 mg, quinidine placebo and intravenous administration of 5 mg/70 kg morphine
D: NKTR-118 25 mg, quinidine 600 mg and intravenous administration of 5 mg/70 kg morphine

Pupil diameter change from baseline: While pupillary measurements were made on both eyes in 4 different conditions: dark (after the volunteer had been dark adapted to the room for 5 minutes), 0.04 lux (scotopic), 0.4 lux (low mesopic), and 4.0 lux (high mesopic), sponsor primarily discusses the findings from the dark light condition as they state that it represents the condition with the highest sensitivity.
The mean peak overall miotic effect in dark condition was 1.09 mm compared to 0.860 mm, 0.729 mm, and 0.430 mm measured in scotopic, low mesopic, and high mesopic conditions, respectively.

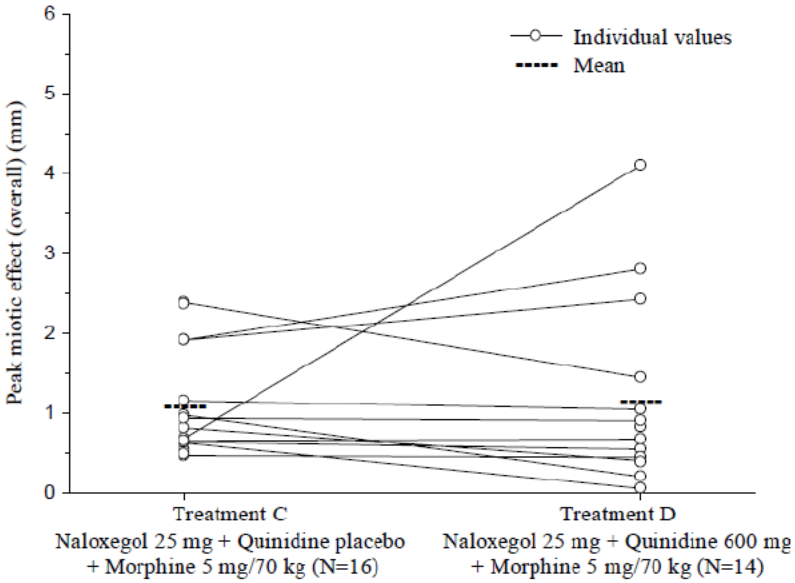
Results from the dark condition showing the mean change from baseline in pupillary measurements for both eyes (overall) at each time point postdose measured in dark condition (after the volunteer had been dark adapted to the room for 5 minutes) are presented in the Figure:



Baseline was defined as the average of 2 separate measurements prior to morphine dose on Day -1 for that period. If only a single assessment existed on Day -1, it was used as a baseline; Change from baseline =Observed value - Baseline value; overall pupil diameter calculated as mean of the assessments of the left and right eye.

Overall, no definite trend for miotic effect changes were noted individuals who received P-gp inhibitor quinidine along with NKTR-118 and morphine; morphine alone group was not included in this study for comparing effect without naloxegol:

Overall Dark



Treatmenta		Light condition			
		Mesopic Hi	Mesopic Lo	Scotopic	Dark
Treatment C	n	17	17	16	16
(N=17)	Mean	0.430	0.729	0.860	1.09
	SD	0.199	0.497	0.447	0.665
	Median	0.360	0.790	0.980	0.870
	Minimum	0.140	0.0100	0.110	0.460
	Maximum	0.770	1.67	1.52	2.38
Treatment D	n	11	12	11	14
(N=14)	Mean	0.300	0.478	0.801	1.16
	SD	0.213	0.337	0.472	1.17
	Median	0.290	0.350	0.580	0.745
	Minimum	0.0200	0.130	0.210	0.0500
	Maximum	0.800	1.09	1.44	4.10

[a] Treatment C: NKTR-118 25 mg plus morphine 5 mg/70 kg iv plus quinidine placebo.
Treatment D: NKTR-118 25 mg plus morphine 5 mg/70 kg iv plus quinidine 600 mg.
iv intravenous; SD standard deviation; Overall: mean of the assessments of the left and right eye. Peak miotic effect defined as maximum pupil diameter decrease from baseline; Baseline defined as Day -1 (average of 2

Mean data suggest some blunting of peak miotic effect (central effect) of morphine in presence of NKTR-118 + Quinidine (i.e. a reduced overall decrease from baseline in pupillary diameter). However, this was not the case for two out of the four conditions tested including Dark condition.

Sponsor conducted the following statistical comparisons for pharmacodynamics (pupillometry):

Sponsor notes that per this exploratory analysis, there were statistically significant decreases in pupil diameter at 2 time points (0.5 and 1 hour) postdose based on the differences in pupil diameters between Treatment D (when NKTR-118 was administered in the presence of quinidine) and Treatment C (when NKTR-118 was administered in

the absence of quinidine); however findings were not adjusted for multiplicity; sponsor also notes that the changes noted at 0.5 and 1 h were in opposite direction to that expected from an antagonism of miosis effect.
Further there was no overall treatment effect.

Statistical comparison of change from baseline overall pupilometry results under dark light condition in the presence or absence of quinidine (Part 2)

					Pairwise comparisons		
Time	**Treatment[a]**	**n**	**LS Mean**	**95% CI**	**Pair**	**Difference**	**90% CI**
Predose	C	16	-0.003	(-0.345, 0.340)	D vs C	0.203	(-0.201, 0.607)
	D	14	0.200	(-0.166, 0.567)			
0.5	C	16	-0.328	(-0.683, 0.027)	D vs C	-0.526	(-0.961, -0.092)
	D	12	-0.854	(-1.261, -0.447)			
1	C	17	-0.383	(-0.799, 0.033)	D vs C	-0.572	(-1.108, -0.037)
	D	11	-0.956	(-1.466, -0.445)			
2	C	17	-0.515	(-0.956, -0.074)	D vs C	-0.088	(-0.645, 0.469)
	D	12	-0.603	(-1.123, -0.083)			
3	C	16	-0.746	(-1.123, -0.368)	D vs C	0.312	(-0.138, 0.762)
	D	13	-0.434	(-0.850, -0.018)			
4	C	16	-0.162	(-0.597, 0.274)	D vs C	-0.499	(-1.018, 0.020)
	D	14	-0.661	(-1.128, -0.195)			
6	C	16	-0.624	(-1.008, -0.241)	D vs C	0.038	(-0.418, 0.493)
	D	14	-0.587	(-0.998, -0.176)			
24	C	17	0.156	(-0.232, 0.544)	D vs C	-0.160	(-0.630, 0.309)
	D	14	-0.004	(-0.431, 0.423)			
Overall	C	17	-0.326	(-0.525, -0.126)	D vs C	-0.162	(-0.374, 0.050)
	D	14	-0.487	(-0.706, -0.269)			

[a] Treatment C: NKTR-118 25 mg plus morphine 5 mg/70 kg iv plus quinidine placebo.
Treatment D: NKTR-118 25 mg plus morphine 5 mg/70 kg iv plus quinidine 600 mg.

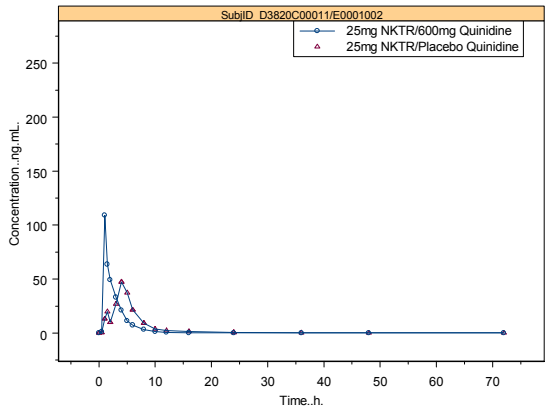
The most prominent impact of Quinidine, a strong P-gp inhibitor drug was found to be on Cmax of naloxegol in this study, which implies potential increase in bioavailability of NKTR-118 due to reduced efflux at the gut level and potentially reduced CYP3A4 clearance as quinidine is also a weak CYP3A4 inhibitor; Sponsor also surmises that increased elimination of NKTR-118, as evidenced by the steeper decline in NKTR-118 concentrations upon quinidine co-administration, could be explained by increased hepatic metabolism of NKTR-118. This increased hepatic metabolism could be as a result of decreased efflux of NKTR-118 into bile due to P-gp inhibition resulting in higher concentrations of NKTR-118 in the hepatocytes for metabolism.

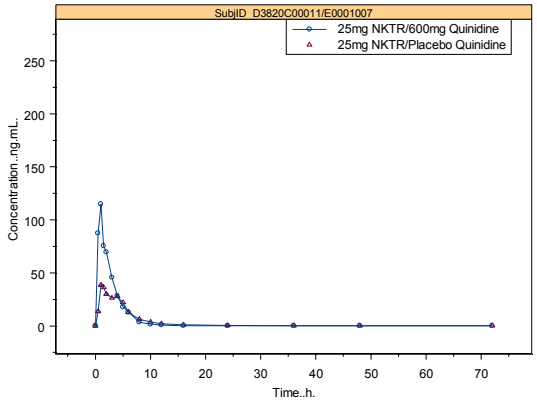
Evaluation of pupilometry assessments as surrogate endpoint for central effects of morphine did not indicate central opioid receptor antagonist pharmacodynamic activity by NKTR-118. During coadministration of NKTR-118 and morphine, the pupillary miotic response appeared to be similar or more pronounced in the presence of quinidine. Thus coadministration of NKTR-118 and quinidine did not antagonize the morphine induced miosis suggesting that Pgp inhibition does not increase the capacity of NKTR-118 to cross the blood-brain barrier at therapeutic doses.

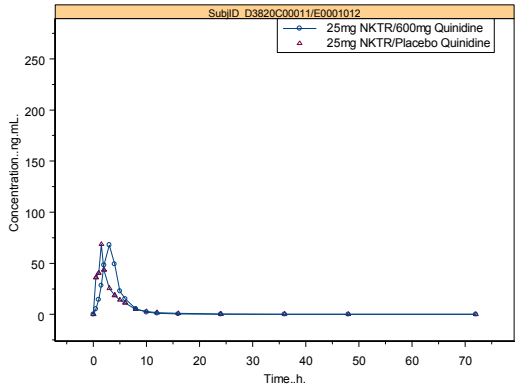
Strong P-gp inhibitors that are also strong CYP3A4 inhibitors will dramatically increase systemic exposures of naloxegol (e.g. 10-13 fold by ketoconazole and therefore contraindicated). However, there are other strong P-gp

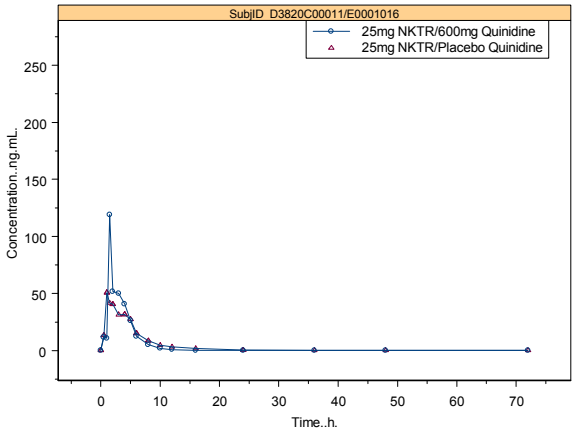
inhibitors such as Quinidine that are only weak inhibitors of CYP3A4 and would have much lower impact on naloxegol exposure changes as noted in this study (2.4 fold increase in Cmax and 1.4 fold increase in AUC).

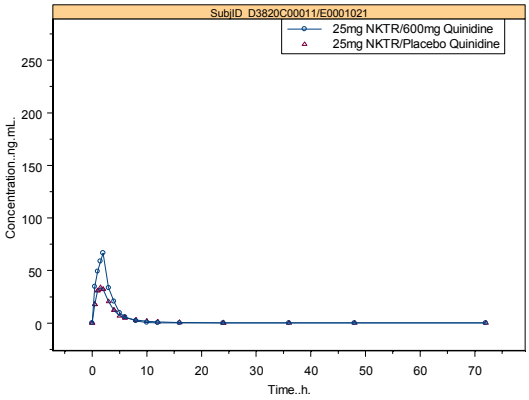
If Cmax of naloxegol is associated with any adverse events, one could consider 12.5 mg BID in presence of Quinidine in order to reduce the Cmax and achieve similar systemic AUC for naloxegol. If high Cmax is not an issue, the current labeling proposal to use standard dose (25 mg QD proposed) in patients who are on (b) (4) weak CYP3A4 inhibitors may be acceptable. (b) (4) moderate CYP3A4 inhibitors (per proposed labeling) will follow dosing for moderate CYP3A4 inhibitors (i.e. 12.5 mg qd); A 2.4-fold higher Cmax is unlikely to be an issue from a QT prolongation perspective, as these levels have been covered in the dose range evaluated in the TQT study which concluded lack of QT prolongation potential at therapeutic (25 mg) and supratherapeutic doses (150 mg).

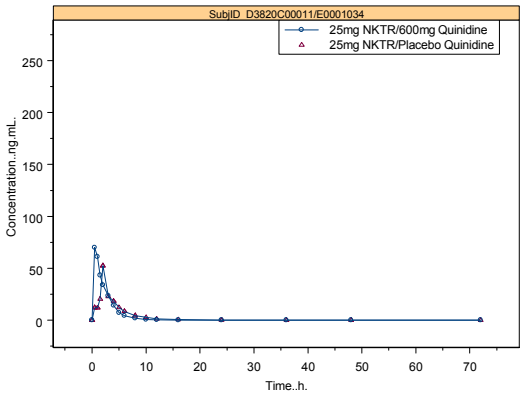


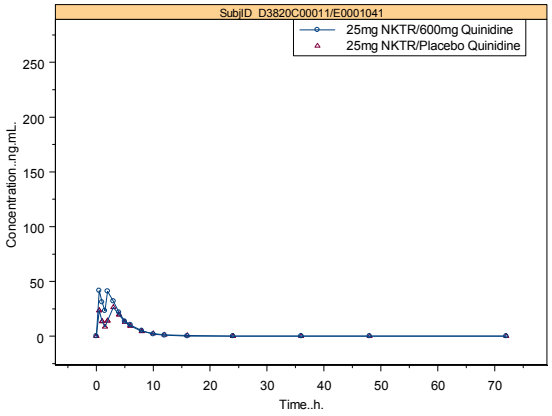


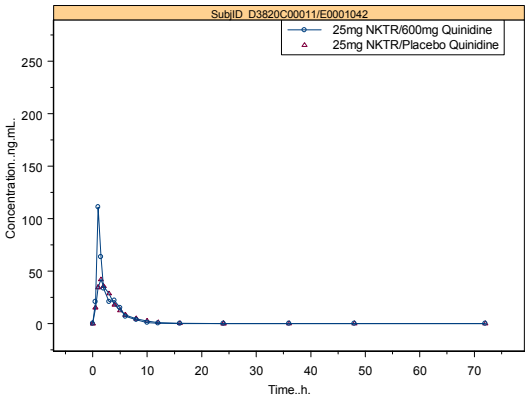


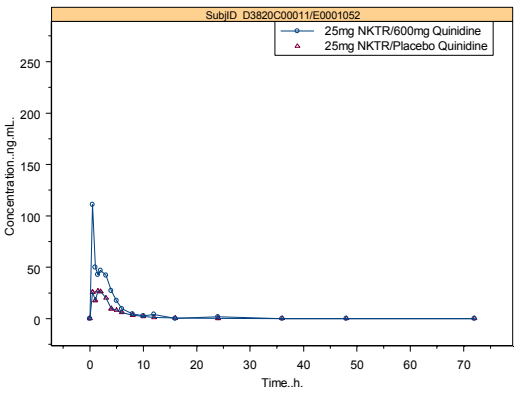


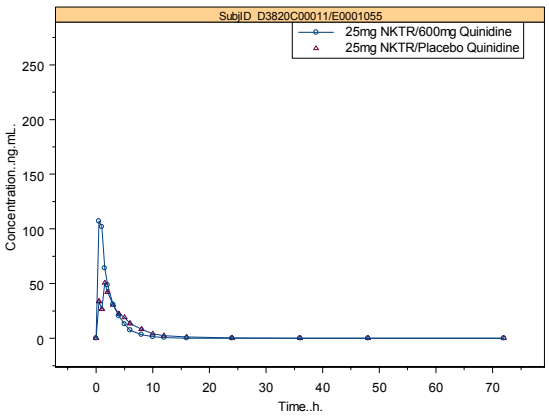

SubjID D3820C00011/E0001021
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

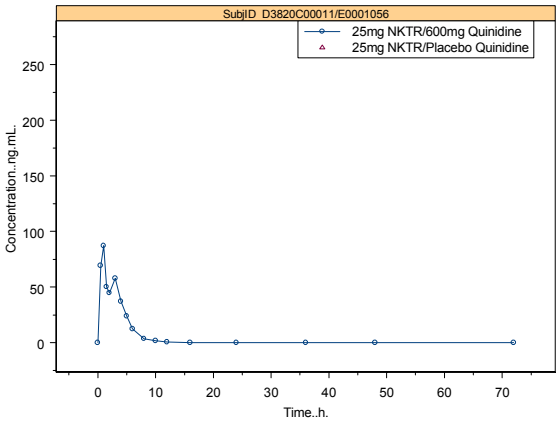

SubjID D3820C00011/E0001034
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

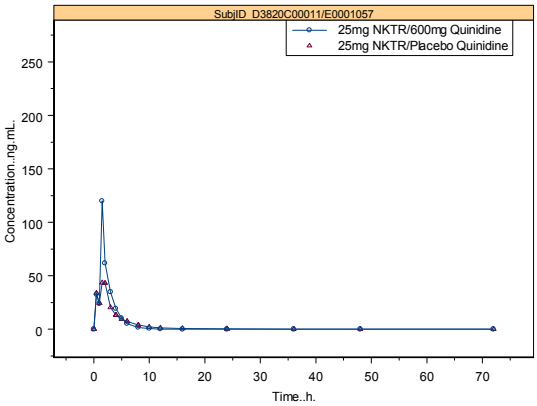

SubjID D3820C00011/E0001041
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

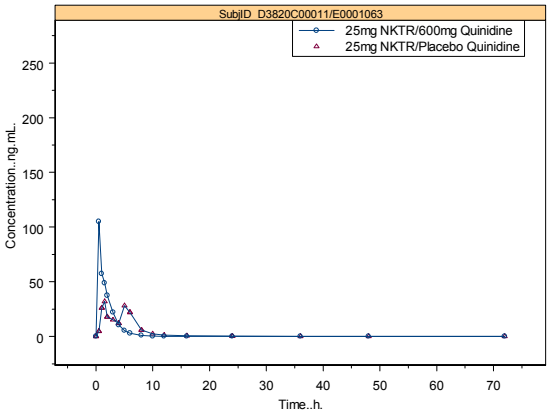

SubjID D3820C00011/E0001042
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

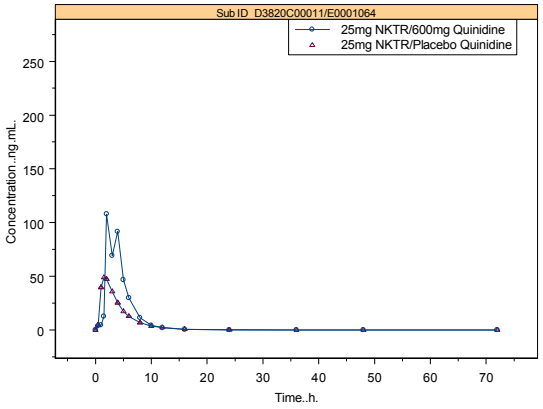

SubjID D3820C00011/E0001052
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

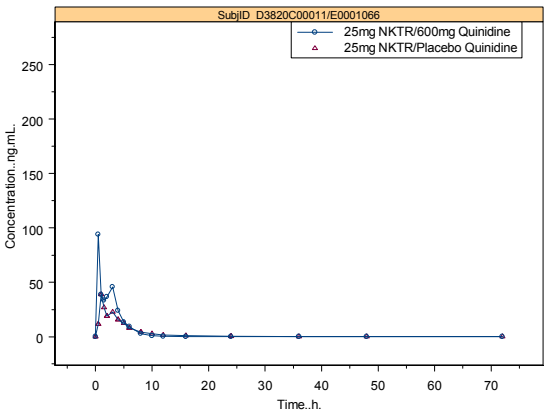

SubjID D3820C00011/E0001055
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

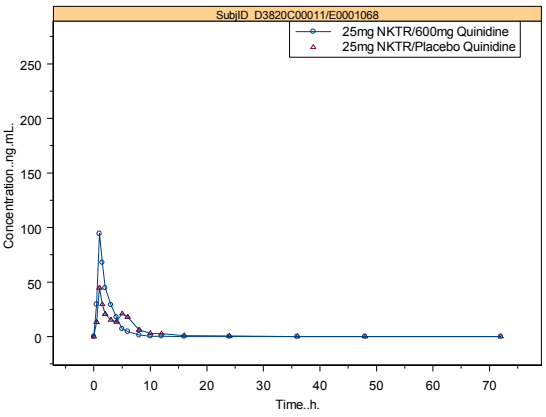


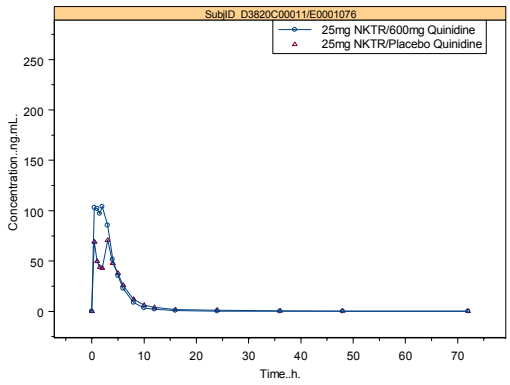


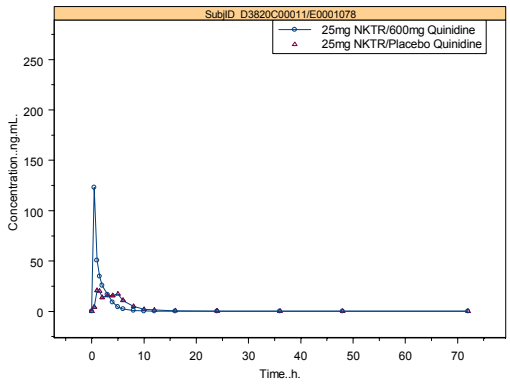


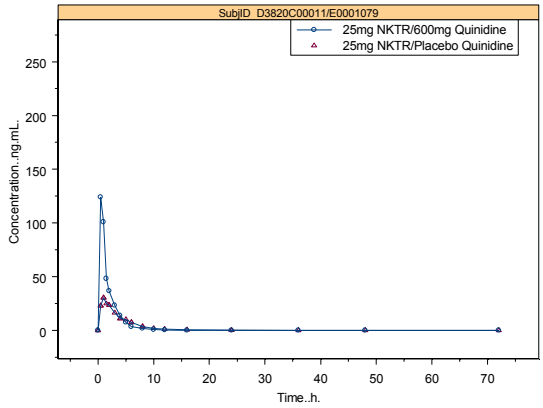


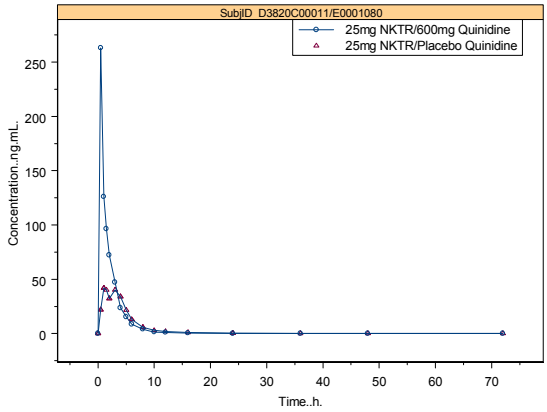


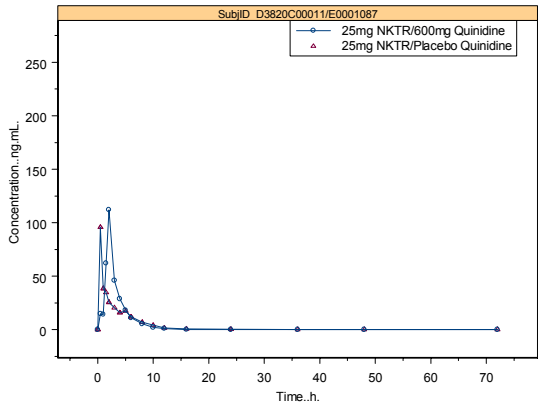


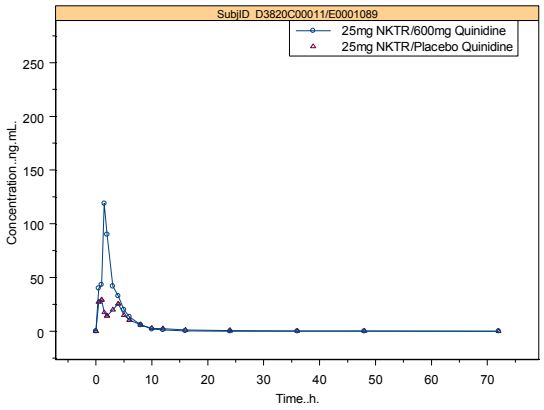

SubjID D3820C00011/E0001076
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

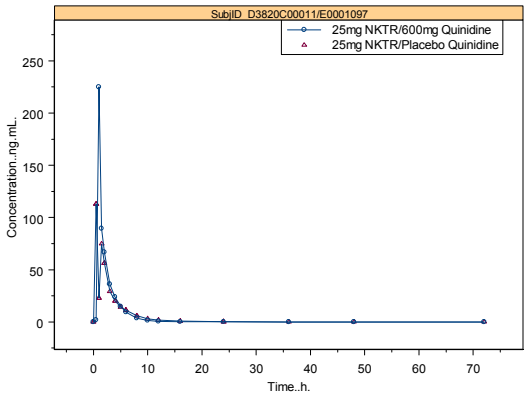

SubjID D3820C00011/E0001078
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

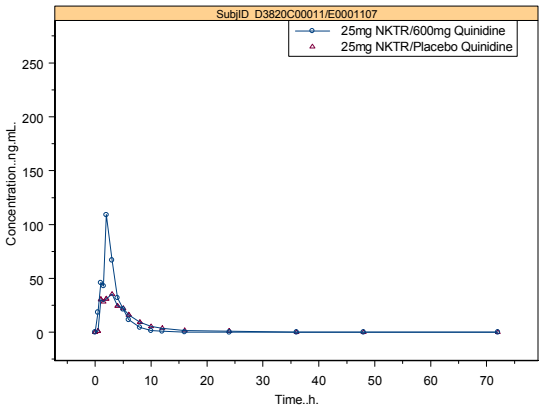

SubjID D3820C00011/E0001079
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

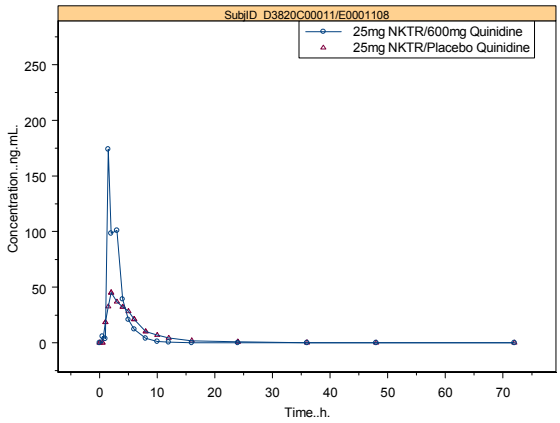

SubjID D3820C00011/E0001080
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

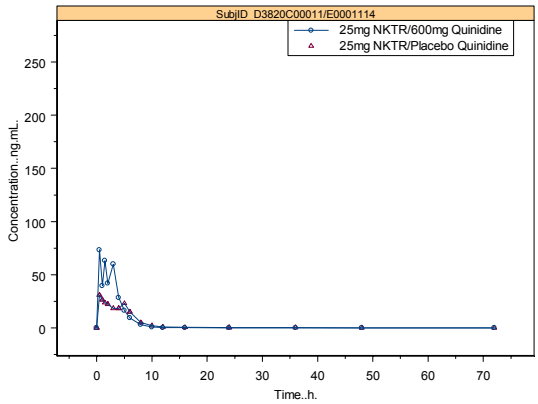

SubjID D3820C00011/E0001087
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

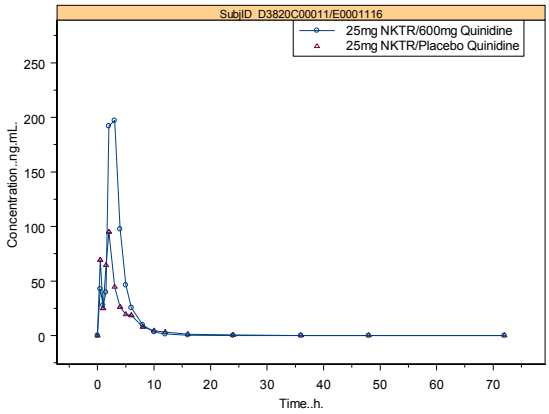

SubjID D3820C00011/E0001089
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

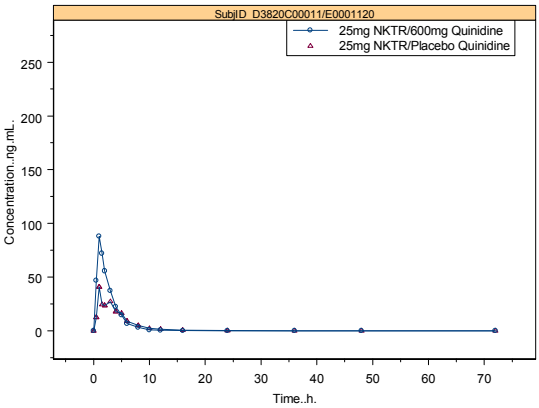

SubjID D3820C00011/E0001097
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

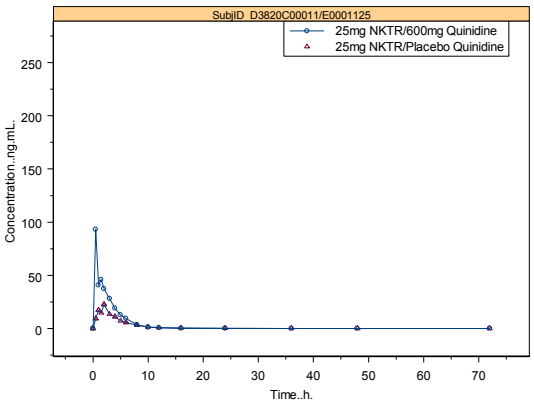

SubjID D3820C00011/E0001107
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

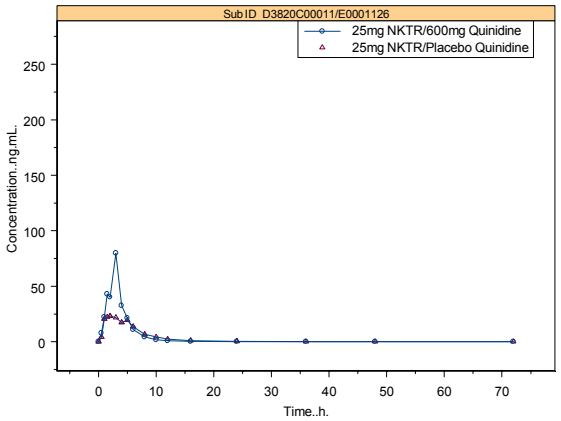

SubjID D3820C00011/E0001108
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

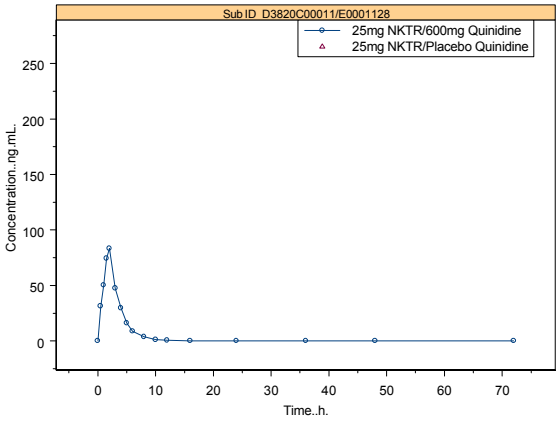

SubjID D3820C00011/E0001114
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

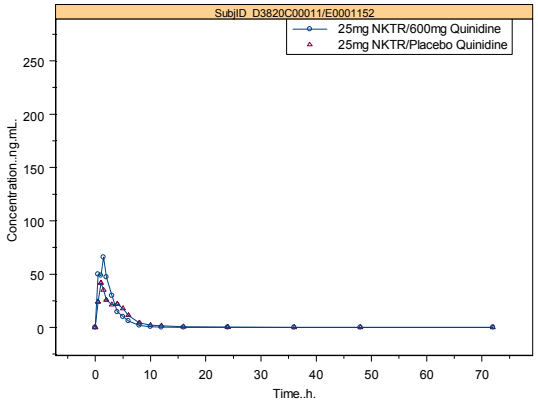

SubjID D3820C00011/E0001116
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

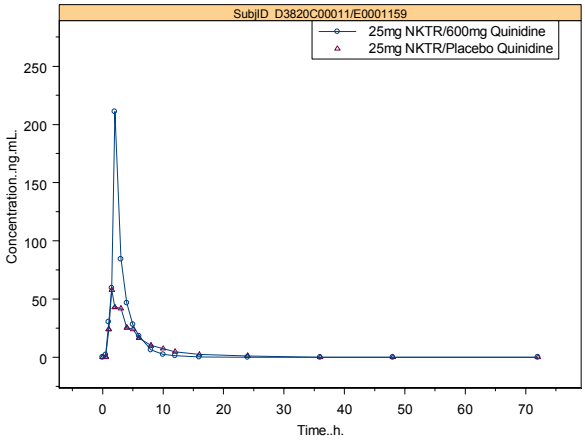

SubjID D3820C00011/E0001120
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

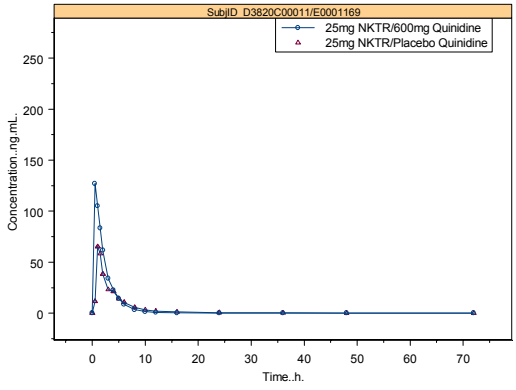

SubjID D3820C00011/E0001125
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

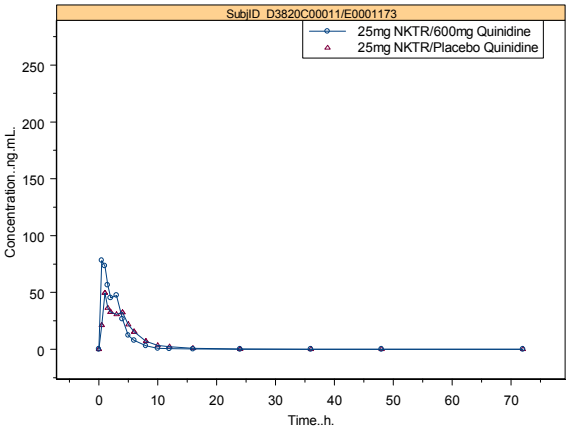

SubID D3820C00011/E0001126
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

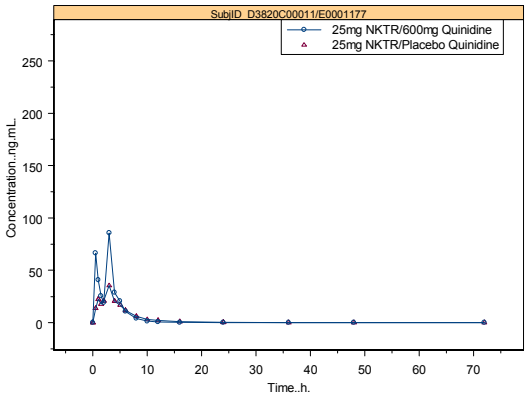

SubID D3820C00011/E0001128
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

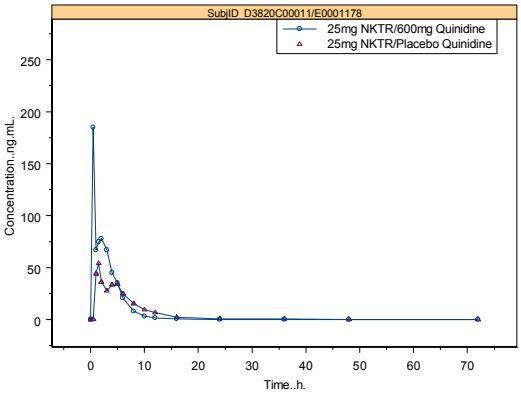

SubjID D3820C00011/E0001152
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

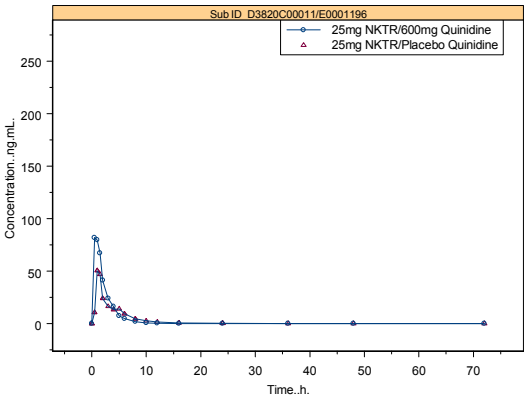

SubjID D3820C00011/E0001159
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.


SubjID D3820C00011/E0001169
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.


SubjID D3820C00011/E0001173
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.


SubjID D3820C00011/E0001177
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.


SubjID D3820C00011/E0001178
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.


Sub ID D3820C00011/E0001196
25mg NKTR/600mg Quinidine
25mg NKTR/Placebo Quinidine
Concentration..ng.mL.
Time..h.

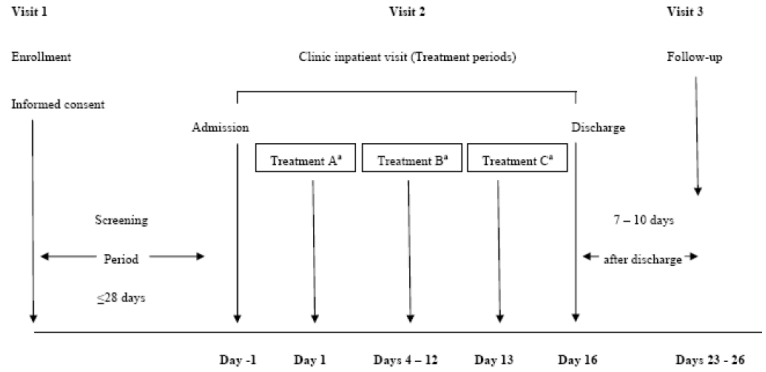
D3820C00015- An Open-label, Fixed-sequence, 3-period, 3-treatment, Crossover Study to Assess the Effects of Rifampin on Pharmacokinetics of NKTR-118 in Healthy Subjects

Design: This was an open-label, fixed-sequence, 3-period, 3-treatment, crossover study to assess the effects of rifampin on the PK of NKTR-118 in healthy volunteers (n =22).

Following a screening period of up to 28 days, volunteers reported to the clinic on Day -1 for admission and assessment of continued eligibility. On Day 1, volunteers received a single oral dose of 25-mg NKTR-118 followed by a 2-day washout (Days 2 and 3). Volunteers received oral doses of 600-mg rifampin once daily for 10 days on the mornings of Days 4 through 12. On Day 13, 25-mg NKTR-118 was co-administered with 600-mg rifampin. A follow-up visit was conducted 7 to 10 days following clinic discharge on Day 16. On PK days (Days 1 and 13), both IPs (Day 13 for rifampin only) were administered in the morning under fasted condition. A meal was allowed 4 hours after dosing.

Serial blood samples for the determination of NKTR-118 concentrations in plasma were collected for 72 hours following NKTR-118 dosing on Days 1 and 13. NKTR-118 PK sampling was done at pre-dose (within 30 minutes prior to drug dosing), 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours post Day 1 and Day 13 NKTR-118 dosing.

Figure 1 Flow chart of study design



[a] Treatment A: NKTR-118 25 mg on Day 1 (Note: Days 2 and 3 were washout period from NKTR-118).
Treatment B: Rifampin 600 mg once daily on Days 4 to 12.
Treatment C: Rifampin 600 mg plus NKTR-118 25 mg on Day 13.

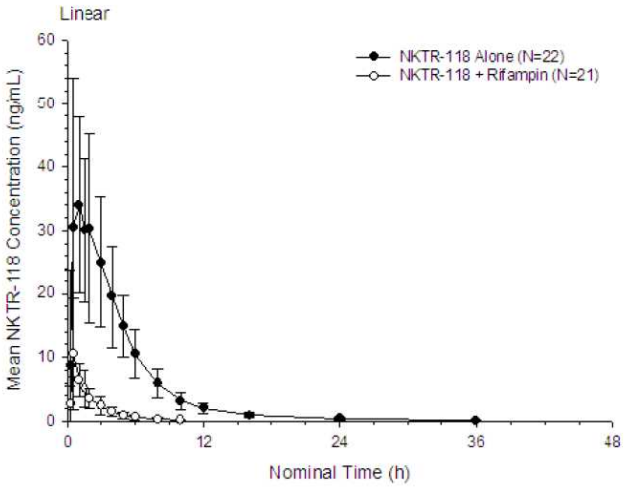
Study objectives and variables measured included the following:

Objective			
Priority	**Type**	**Description**	**Description**
Primary	Pharmacokinetic	To investigate the effect of rifampin on the PK of NKTR-118 in healthy subjects	AUC, C_{max}, t_{max}, $t_{1/2\lambda z}$, λ_z, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}8)}$; $AUC_{(0\ 24)}$, CL/F, and V_z/F
Secondary	Safety	To assess the safety and tolerability of NKTR-118 when administered alone and in combination with rifampin	AEs, clinical laboratory assessments, vital signs, physical examinations, ECGs, and C-SSRS
Exploratory[a]		To collect plasma samples for potential NKTR-118 metabolite analysis	

Statistical analysis: To address the primary objective of the study, the effect of 600-mg rifampin on the PK of 25-mg NKTR-118 was assessed using a linear mixed-effect analysis of variance model for the PK parameters AUC and Cmax on log-scale. An additional parameter, AUC(0-8) was also analyzed in a similar manner. Plasma

concentrations beyond 8 hours postdose fell below LLOQ (0.100 ng/mL) in many of the volunteers receiving both NKTR-118 and rifampin and by 12 hours postdose NKTR-118 was quantifiable in only 3 out of 21 volunteers. Hence AUC(0-8) was the longest "shared" AUC for all volunteers which could be directly compared across the 2 treatments. Treatment was included as a fixed effect and volunteer was included as a random effect in the model. Geometric least-squares (LS) means by treatment with 95% confidence intervals (CI), and geometric LS means ratios for the treatment effect NKTR-118 plus rifampin (test), versus NKTR-118 alone (reference) with 2-sided 90% CI were presented for AUC and Cmax. If the 90% CIs were completely contained within the pre-specified limits (70% to 143%) then no effect of rifampin on the PK of NKTR-118 would have been concluded.

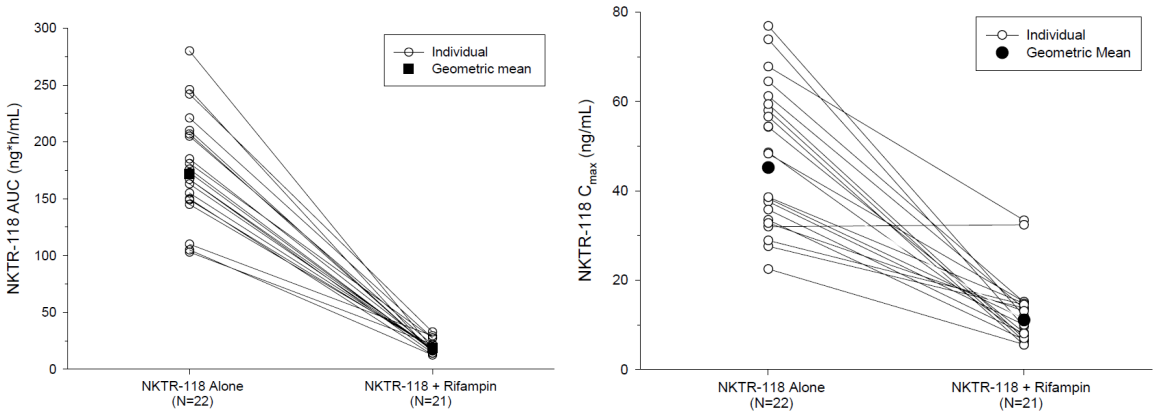
Results: The mean plasma concentration-time profiles for naloxegol with or without CYP3A4 inducer rifampin are shown below; plasma concentrations decreased markedly in presence of rifampin;



Summary arithmetic mean PK parameters are presented for Naloxegol without and with rifampin:

Arithmetic mean ± SD	Naloxegol alone (n = 22)	Naloxegol + rifampin (N= 21)
Cmax (ng/mL)	47.8 ± 15.9	12.6 ±7.5
AUC0-t (ng h/mL)	175 ± 45	18.9 ± 5.5
AUC0-inf (ng.h/mL)	177 ± 45	19.4 ± 5.6
AUC0-8 (ng.h/mL)	148 ± 40	18.6 ± 5.1
AUC0-24 (ng.h/mL)	173 ± 45	19.1 ± 5.6
Tmax (h)	1.0 [0.25-4.0]	0.5[0.25-1.5]
T1/2 (h)	7.65 ± 5.26	1.87 ± 0.38
CL/F (L/h)	150 ± 42	1380 ± 346
Vz/F (L)	1660 ± 1200	3690 ± 1120

Data suggests that in presence of strong CYP3A4/P-gp inducer drug rifampin, both Cmax and AUC of naloxegol, a substrate of both CYP3A4 and P-gp were markedly reduced. The clearance of naloxegol was markedly higher likely due to induction of CYP3A4 mediated gut and systemic metabolism as well as increased efflux by P-gp transporter at the gut and/or biliary level. The half-life value of naloxegol was also markedly reduced in presence of rifampin.



Statistical analyses: Data table below summarizes the point estimates of the geometric LS mean ratios and associated 90% CIs for the NKTR-118 primary PK parameters, AUC and Cmax and an additional PK parameter AUC(0-8); data suggests a statistically significant effect of rifampin on naloxegol PK. Overall, the decrease in naloxegol Cmax, AUC, AUC0-8 in presence of rifampin were 76 %, 89 %, and 87 % respectively.

					Comparisons		
Parameter	**Treatment[a]**	**n**	**Geometric LS mean**	**95% CI**	**Pair**	**Ratio (%)**	**90% CI**
AUC	A	22	171.8	(153.2, 192.6)			
(ng·h/mL)	C	21	18.72	(16.65, 21.05)	C/A	10.90	(9.54%, 12.45%)
C_{max}	A	22	45.20	(37.61, 54.32)			
(ng/mL)	C	21	11.06	(9.160, 13.36)	C/A	24.47	(19.63%, 30.51%)
$AUC_{(0-8)}$[b]	A	22	142.6	(127.1, 160.0)			
(ng·h/mL)	C	21	17.93	(15.94, 20.17)	C/A	12.57	(11.01%, 14.36%)

[a] Treatment A: 25-mg NKTR-118 on Day 1.
Treatment C: 600-mg rifampin plus 25-mg NKTR-118 on Day 13
[b] $AUC_{(0-8)}$ was an additional PK parameter added to the analysis.

D3820C00009- An Open-Label, Parallel-Group, Phase I Study to Compare the Pharmacokinetics of NKTR-118 (Naloxegol) Following a Single Oral Dose in Subjects with Renal Impairment and Subjects with Normal Renal Function

Methods: This study was conducted to evaluate the effects of renal impairment and hemodialysis on the PK and safety/tolerability of naloxegol, a peripheral mu-opioid receptor antagonist developed for opioid induced constipation.

The primary objective was to investigate the PK of a single 25 mg oral dose of Naloxegol in subjects with renal impairment compared to that in subjects with normal renal function. Secondary objectives involved assessment of safety and tolerability in these populations. As an exploratory objective, plasma, urine and dialysate samples were collected for potential metabolite analysis.

Study design involved an open-label, single-dose, parallel group study in a total of 32 male and female subjects (n = 8 per cohort) belonging to the following groups: 1) normal renal function 2) moderate renal impairment, 3) severe renal impairment, and 4) end-stage-renal disease (ESRD requiring hemodialysis). Sponsor notes that since subjects with mild renal impairment were enrolled in the Phase 3 program, this population was not included in the current study. Four subjects in Group 3 (subjects with severe renal impairment: E0001001, E0001005, E0002010, and E0002016) had an estimated eGFR of less than 15 mL/min/1.73m2. This specification meets the subgroup of ESRD subjects with eGFR "less than 15 mL/min/1.73m2 not on dialysis".

Subjects with normal, moderate or severe renal impairment received a single 25 mg dose and pharmacokinetic blood and urine sampling was done for 72 hours after dosing. Subjects with ESRD requiring hemodialysis participated in two treatment periods; the first dose was given ~1 to 2 hours after completion of a hemodialysis session while in the second treatment period (separated by a washout of 7 days), another single 25 mg dose was given 1- 2 hours before the start of hemodialysis (with the aim of performing hemodialysis around the Tmax of the drug). PK and urine sampling was done for 72 hours after each dose. In the second treatment period PK samples were obtained throughout the hemodialysis session.

Sampling details: The PK blood sampling times for Groups 1 to 3, and for Group 4 in Treatment Periods 1 and 2 were: pre-dose, 30 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours post-dose. However, in Treatment Period 2 for Group 4, the sample scheduled for collection at 2 hours had to be collected immediately before hemodialysis start and the sample scheduled at 6 hours had to be collected immediately before hemodialysis completion.

Group 4 Treatment Period 2: Subjects started their scheduled hemodialysis at 2 hours after the NKTR-118 administration. Dialysate was collected over 1-hour intervals throughout the entire (approximately 4-hour) hemodialysis session (e.g., 0 to 1, 1 to 2, 2 to 3, and 3 to 4 hours, which corresponds to approximately 2 to 3, 3 to 4, 4 to 5, 5 to 6 hours post-dose).

Urine PK samples were collected in Groups 1 to 3 for 72 hours after the morning dose in the following intervals: pre-dose, 0 to 12, 12 to 24, 24 to 48 and 48 to 72 hours post-dose. This collection was optional for subjects in Group 4, as subjects on hemodialysis usually do not have urine excretion.

PK variables: The primary variables were NKTR-118 AUC and Cmax; Secondary variables were NKTR-118 AUC(0-t), AUC(0-24), CL/F, Vz/F, tmax, and t1/2; urine NKTR-118 Ae, fe, and CLR; dialysate f_D and CL_D. Pharmacokinetic parameters were derived using standard noncompartmental methods with WinNonlin® Professional version 5.2 or higher (Pharsight Corp., Mountain View, California, United States). The PK and safety summaries and data listings as well as the statistical analysis of the PK variables were prepared using SAS® version

9.2 (SAS Institute, Inc., Cary, North Carolina, United States). Figures of PK data were prepared using SAS® version 9.2 or SigmaPlot® 9.0 (Systat Software, Inc., San Jose, California, United States).

Calculations: The degree of renal impairment was evaluated based on renal function calculated by the abbreviated 4-variable Modification of Diet in Renal Disease (MDRD) equation (National Kidney Foundation 2002) using measured serum creatinine values:

$$\text{eGFR (in mL/min/1.73m}^2\text{)} = 175 \times (\text{serum creatinine in mg/dL})^{-1.154} \times \text{age in years}^{-0.203} \times (1.210 \text{ if African American}) \times (0.742 \text{ if female})$$

Definitions used for identifying renal function status based on eGFR (MDRD) were as follows:

Group	Description	eGFR (mL/min/1.73m^2)
Group 1	Normal renal function	≥80
Group 2	Moderate renal impairment	30 to 59 (inclusive)
Group 3	Severe renal impairment	less than 30
Group 4	ESRD	requiring hemodialysis

PK data were presented by renal function group using the primary classification of eGFR determined by the MDRD formula. In addition, a tabular summary of PK parameters was presented based on an estimate of the subjects' creatinine clearance (CLCr) derived using the Cockcroft-Gault (C-G) equation (Cockcroft and Gault 1976), using the following formulas:

For males:

- CL_{Cr} (mL/min) = {[(140-age(years)] × weight(kg)} / 72 × serum creatinine (mg/dL)

For females:

- CL_{Cr} (mL/min) = {[(140-age(years)] × weight(kg)} / 72 × serum creatinine (mg/dL) × 0.85

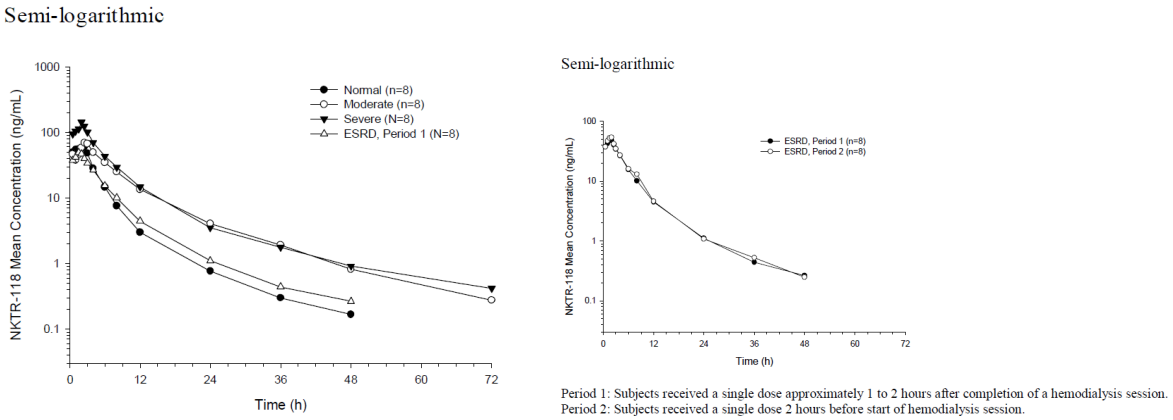
In addition, figures which plotted individual PK parameters versus eGFR values based on MDRD were also plotted versus CLCr calculated using the C-G equation.

Regression models were used to assess and quantify the relationship between renal function, as measured by the eGFR, and NKTR-118 primary PK parameters (Cmax and AUC). The initial model specified a linear relationship between primary PK parameters and the eGFR, and was estimated using ordinary least squares. Log-transformations were used to improve model fit. Nonlinear models were to be used in the event that linear models did not yield an adequate fit. Model parameters, their standard errors, 90% confidence intervals (CIs) and p-values were reported. From the final models, the predicted PK parameters were estimated at each of the observed eGFR values. Prediction error estimates and their 90% CIs were to be provided.

Comparisons of PK parameters for subjects with ESRD on a non-hemodialysis day to those on a hemodialysis day were performed using a paired t-test (Cmax and AUC). Means, corresponding 90% CIs and p-values were presented.

Protocol deviations: A planned prediction of PK parameters from regression models was not performed as the regression models showed poor fit of the data. 2 subjects assigned to the Normal renal function group who had screening and Day -1 eGFR values below 80 mL/min/1.73m2 (values of 74 and 76 mL/min/1.73m2); hence, eGFR results are presented with and without these subjects.

Results: Arithmetic mean plasma concentrations (ng/mL) of NKTR-118 versus time by treatment after single 25-mg oral NKTR-118 dose are shown for all renal function categories (MDRD); Also shown on the right hand panel is the comparison of plasma concentrations in ESRD subjects who received drug either 1-2 h after HD (period 1) or 1-2 h before HD (period 2); concentrations were similar in both cases in the ESRD patients and were comparable to normal subjects.



Period 1: Subjects received a single dose approximately 1 to 2 hours after completion of a hemodialysis session.
Period 2: Subjects received a single dose 2 hours before start of hemodialysis session.

A summary of arithmetic mean PK data (mean ± SD) classified by eGFR (MDRD):

	Normal (n= 8)	Normal (N=6)*	Moderate RI (n = 8)	Severe RI (n = 8)	ESRD post-HD (n = 8)	ESRD Pre – HD (n = 8)
Cmax (ng/mL)	83 ± 44	90 ± 49	94 ± 38	176 ± 122	63 ± 31	71 ± 30
AUC_{0-t} (ng.h/mL)	299 ± 114	301 ± 131	577 ± 394	822 ± 797	284 ± 95	292 ± 97
Tmax (h); median (range)	1.25 (0.5 – 2.5)	1.25 (0.5-2.5)	2.00 (0.5-3.0)	1.50 (0.5 -2.0)	1.25 (0.5-2.5)	1.25 (0.5-2.0)
T1/2 (h)	11.8 ± 7.9	8.9 ± 3.4	11.9 ± 5.4	12.3 ± 8.1	11.4 ± 7.3	9.2 ± 4.5
Cl/F (L/h)	93 ± 34	95 ± 39	60 ± 33	50 ± 27	100 ± 46	93 ± 32
Vz/F (L)	1410 ± 791	1110 ± 436	1140 ± 1300	773 ± 686	1520 ± 942	1200 ± 674
CL_R (L/h)	4.7 ± 2.7	5.4 ± 2.5	3.5 ± 1.1	1.2 ± 0.6	ND	ND

*Excluding data from subjects E0002025 and E0002026 who were mis-classified as Normal.

```
Normal renal function: eGFR >=80; single oral dose of 25 mg NKTR-118 on Day 1;
Moderate renal impairment: eGFR 30 to 59 inclusive; single oral dose of 25 mg NKTR-118 on Day 1;
Severe renal impairment: eGFR less than 30; single oral dose of 25 mg NKTR-118 on Day 1;
End stage renal disease (ESRD): requiring hemodialysis; 7 day washout between treatment periods:
          Treatment Period 1: single oral dose of 25 mg NKTR-118 on Day 1, 1 to 2 hours after completion of hemodialysis;
          Treatment Period 2: single oral dose of 25 mg NKTR-118 on Day 1, 2 hours before start of hemodialysis.
```

A summary of arithmetic mean PK data (mean ± SD) grouped by Clcr data (Cockroft-Gault):

	Normal (n= 9)	Mild (N=3)	Moderate RI (n = 6)	Severe RI (n = 6)	ESRD post-HD (n = 8)	ESRD Pre – HD (n = 8)
Cmax (ng/mL)	83 ± 41	113 ± 60	151 ± 148	139 ± 62	63 ± 31	71 ± 30
AUC_{0-t} (ng.h/mL)	325 ± 132	615 ± 614	859 ± 855	609 ± 473	284 ± 95	292 ± 97
Tmax (h); median (range)	1.00 (0.5- 2.5)	1.50 (0.5 -3.0)	2.00 (2.0-3.0)	0.75 (0.5-2.0)	1.25 (0.5-2.5)	1.25 (0.5-2.0)
T1/2 (h)	11.4 ± 7.5	15.8 ± 7.6	10.3 ± 2.6	12.6 ± 9.4	11.4 ± 7.3	9.2 ± 4.5
Cl/F (L/h)	88 ± 36	73 ± 53	47 ± 24	55 ± 25	100 ± 46	93 ± 32
Vz/F (L)	1320 ± 788	1900 ± 2100	630 ± 264	868 ± 762	1520 ± 942	1200 ± 674
CL_R (L/h)	4.7 ± 2.6	3.4 ± 1.4	2.8 ± 1.0	1.0 ± 0.5	ND	ND

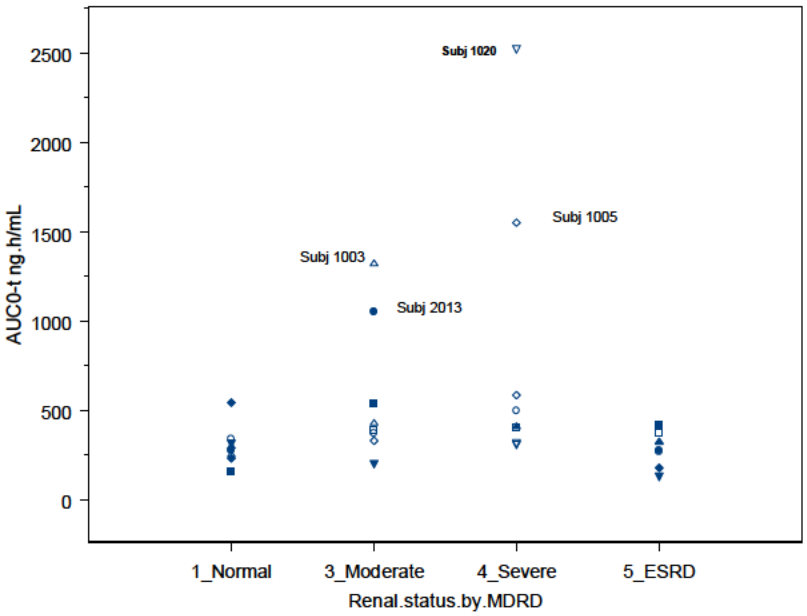
Renal function group determined by Cockcroft-Gault equation.
Normal renal function: CLCR >=80; single oral dose of 25 mg NKTR-118 on Day 1;
Mild renal impairment: CLCR 60 to 79 inclusive; single oral dose of 25 mg NKTR-118 on Day 1;
Moderate renal impairment: CLCR 30 to 59 inclusive; single oral dose of 25 mg NKTR-118 on Day 1;
Severe renal impairment: CLCR less than 30; single oral dose of 25 mg NKTR-118 on Day 1;
End stage renal disease (ESRD): requiring hemodialysis; 7 day washout between treatment periods:
Treatment Period 1: single oral dose of 25 mg NKTR-118 on Day 1, 1 to 2 hours after completion of hemodialysis;
Treatment Period 2: single oral dose of 25 mg NKTR-118 on Day 1, 2 hours before start of hemodialysis.

Initial screening and baseline renal classification was by eGFR by MDRD; later on sponsor also evaluated renal classification by creatinine clearance values as calculated by CG formula. Most patients remained in the same category of renal function when evaluated by either MDRD or CG classification (26/32 subjects; particularly no change in classification was noted for subjects who were classified as normal or ESRD), while differences in renal function group were noted for some subjects originally classified as moderate (4/8) or severe (2/8) when re-grouped by CG:

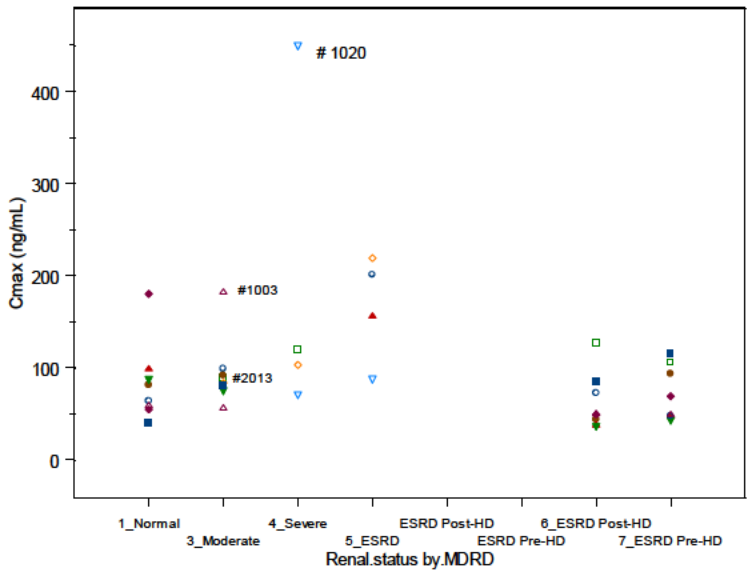
Change in 3/8 moderate to mild and 1/8 moderate to normal (MDRD to CG); no change in 4; Change in 2/8 severe to moderate (MDRD to CG); no change in 6.

When classified by MDRD method, two individuals each in the moderate and severe renal impairment groups appear to have markedly higher systemic exposures compared to others in the groups and drive up the average exposure parameters for their respective renal groups (see the outliers in the AUC scatter plot below per sponsor's original grouping).

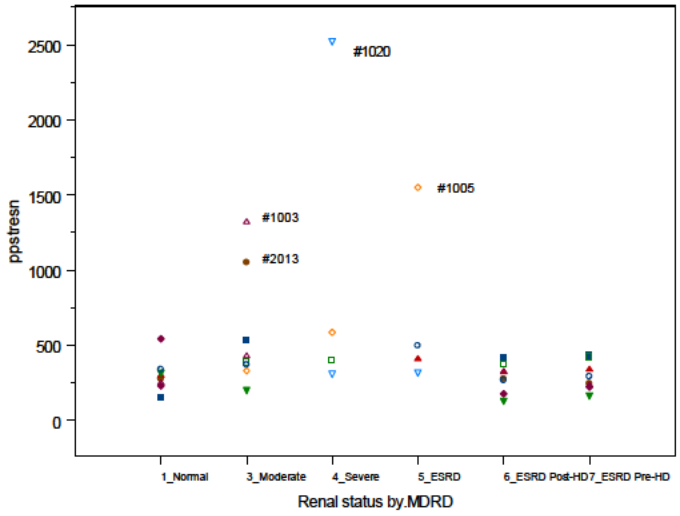
When classified by CG method, one individual in mild, two in moderate and one in severe group appear to have higher AUC compared to others in the groups.

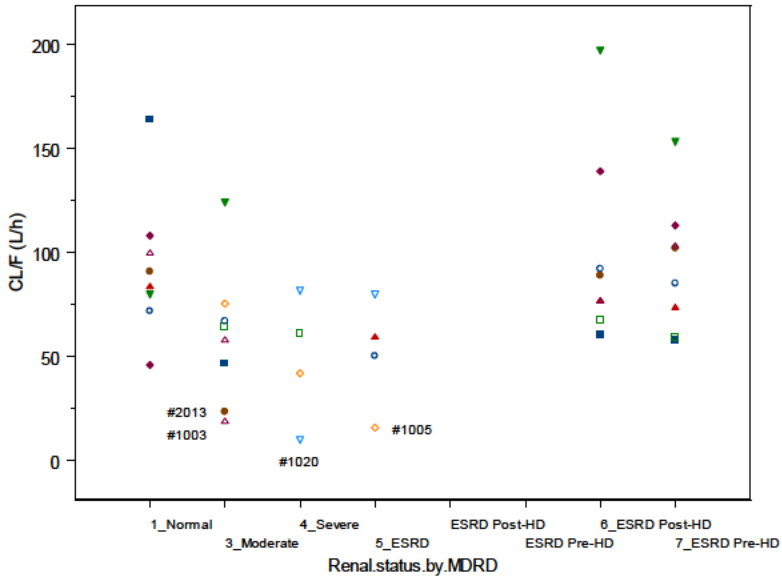


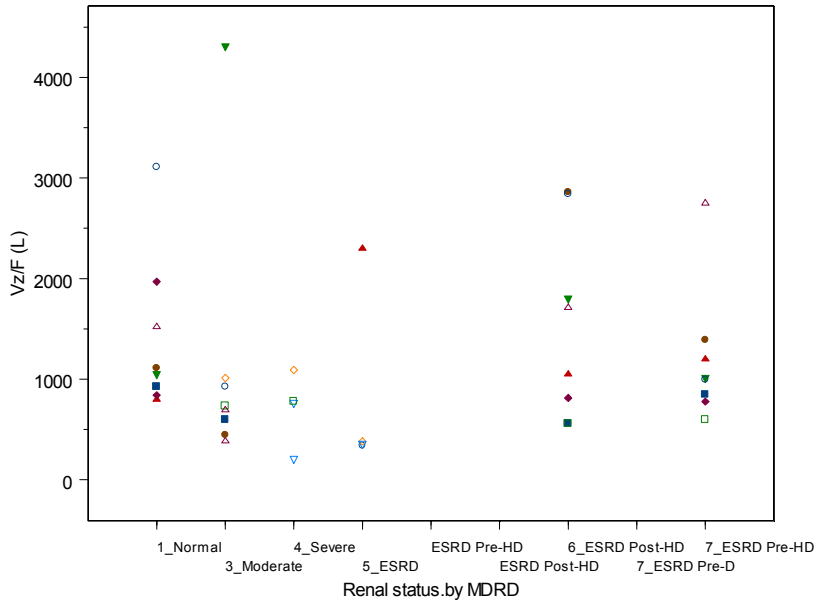
Because 4 patients in the severe group actually were classified to be ESRD (not on dialysis) by MDRD, scatter plots below are presented by further grouping the Severe group into severe (n =4) and ESRD (n =4):



AUC scatter plot





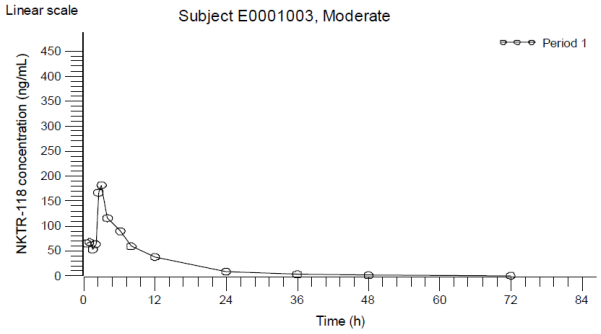


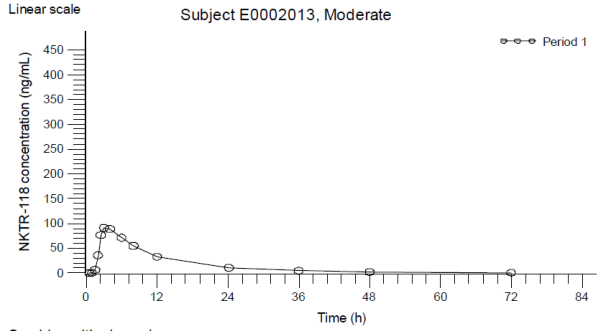
Compared to the average exposures noted in the control group, the systemic exposures in the four individual outliers were 2 - 5 fold higher for Cmax and 3.5-8.4 fold higher for AUC. T1/2 values in these four subjects (1003, 1005, 1020 ad 2013) were 14.1 h, 16.6 h, 13.8 h and 13.8 h, respectively, compared to the average T1/2 in control subjects of 11.8 ± 7.9 h. The sponsor provided a summary of the demographics, clinical characteristics of these potential 'outliers' (MDRD classification) noting that there was nothing clinically remarkable about these four individuals who demonstrated higher than typical PK exposures. Review of the data provided suggests that their age, BMI, co-existing conditions (e.g. diabetes) and concomitant medications (some of which did appear to be weak CYP3A4 inhibitors) have been noted in other study subjects as well without a similar impact on exposures. The Bioanalytical report suggests acceptable assay precision and accuracy; the four subjects showed pre-dose values below detection but higher post-dose values at most time-points, compared to other individuals in the groups; C-t profiles suggest either higher Cmax values or sustained concentrations compared to other subjects in the study;

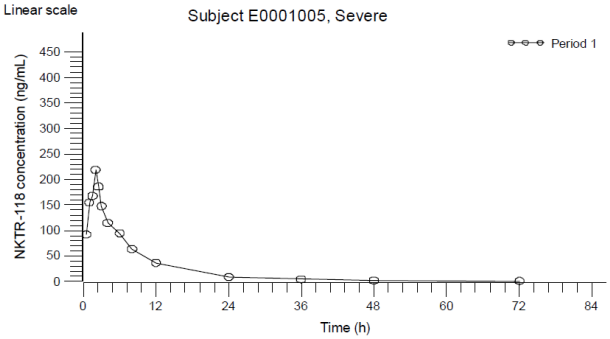
Subject/ classification/ Day -1 eGFR	PK parameters	Ratio - compared to[a]:	Demographics – age, sex, race, BMI	Medical history of metabolism and nutrition disorders	Concomitant medications
E0001003 Moderate 44 mL/min/1.73m^2	AUC: 1330 ng*h/mL C_{max}: 182 ng/mL f_e: 11.3 %	mod – 2.73 norm – 4.73 mod – 2.04 norm – 2.26	60 years, male, white, 31 kg/m^2	type 2 diabetes mellitus	acetylsalicylic acid, 81 mg BID clopidogrel, 75 mg QD glipizide, 5 mg BID carvedilol, 25 mg BID
E0002013 Moderate 42 mL/min/1.73m^2	AUC: 1060 ng*h/mL C_{max}: 91.4 ng/mL f_e: 9.11 %	mod – 2.18 norm – 3.77 mod – 1.02 norm -- 1.14	55 years, male, white, 27 kg/m^2	type 2 diabetes mellitus	amlodipine, 10 mg QD glipizide, 5 mg BID hydrochlorothiazide 25 mg QD omeprazole, 20 mg QD
E0001005 Severe 13 mL/min/1.73m^2	AUC: 1580 ng*h/mL C_{max}: 219 ng/mL f_e: 2.79 %	sev – 2.58 norm – 5.62 sev – 1.48 norm – 2.72	61 years, male, white, 22 kg/m^2	type 2 diabetes mellitus gout hypercolesterolaemia hyperkalaemia hypersphosphataemia vitamin D deficiency	acetylsalicylic acid, 81 mg QD fish oil, 2000 mg QD gabapentin, 300 mg prn carvedilol, 40 mg BID bumetanide, 1 mg prn allopurinol, 100 mg QD alprazolam, 0.25 mg prn xantofyl, 6 mg QD multivitamins, 1 tablet QD calcium acetate 667 mg TID sodium bicarbonate 650 mg prn
E0001020 Severe 24 mL/min/1.73m^2	AUC: 2530 ng*h/mL C_{max}: 449 ng/mL f_e: 13.1 %	sev – 4.13 norm – 9.00 sev – 3.03 norm – 5.58	66 years, male, white, 26 kg/m^2	gout	allopurinol, 100 mg QD rosuvastatin, 5 mg QD paracetamol, 500 mg prn amlodipine, 10 mg QD iron, 325 mg TID hydralazine, 100 mg TID imipramine, 10 mg QD terazosin, 4 mg BID cyanocobalamin, 500 mg QD ascorbic acid, 500 mg QD

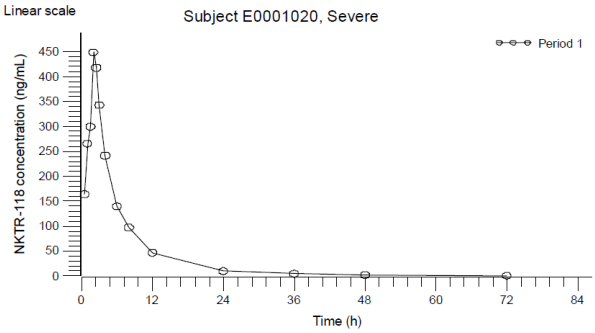
BID twice daily; mod moderate; norm normal; prn as needed; QD once daily; sev severe; TID 3 times daily.
[a] Individual subject PK parameter (AUC and C_{max}) is compared to the geometric mean for that subject's group and compared to the geometric mean of the normal group (n=6). Value presented is ratio of individual value compared to the mean.

The individual plasma-concentration time profiles are shown for these four subjects:



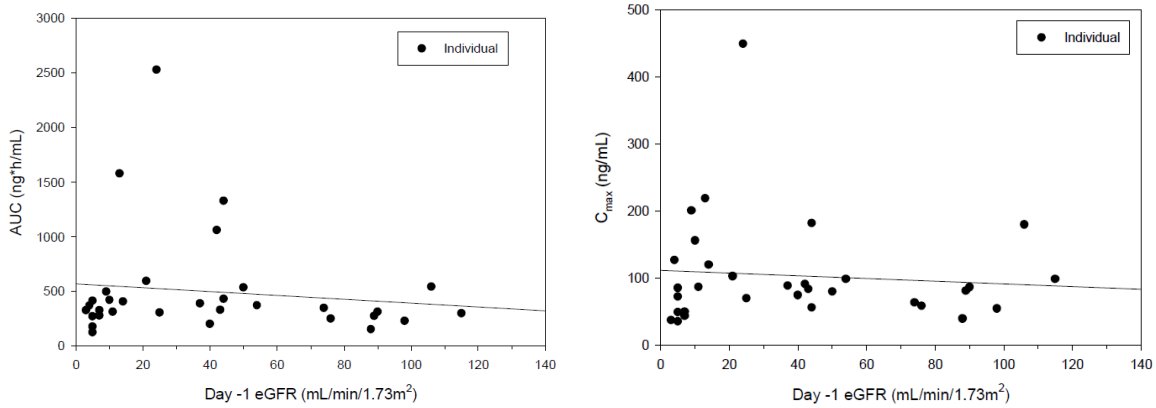






It is likely that these subjects may have experienced higher exposures potentially due to impact of decreased renal function on the metabolism (CYP3A4) or transport (P-gp or other) of the drug at the gut or liver. However, it is still unclear as to why renal impairment had a differential effect on these four individuals compared to others in the study; further elaboration is needed, especially on the issue of concomitant medications (timing relative to naloxegol), and transporters other than P-gp may be needed to understand this. Sponsor was unable to provide additional information in this regard upon seeking further clarification. With 25 % of the total subjects with moderate to severe renal impairment (4/16), demonstrating higher exposures, it is not possible rule these out as outliers.

No significant correlation was noted between renal function and exposures (sponsors plots):



Renal clearance (CLr) appeared to decrease with increasing severity of renal impairment. In subjects with severe renal impairment the mean fraction of drug excreted in urine (fe) of 2.40% was lower than in normal subjects (5.22%) and subjects with moderate renal impairment (6.43%).

Parameter		Normal[a] (n=6)	Normal[b] (n=8)	Moderate (n=8)	Severe (n=8)	ESRD, Period 2[c] (n=8)
CL_R (L/h)	Geo Mean	4.74	3.53	3.38	1.05	ND
	CV%	64.6	129.7	33.2	57.8	
f_e (%)	Geo Mean	5.22	3.86	6.43	2.40	ND
	CV%	66.0	148.5	53.6	103.8	
CL_D (L/h)	Geo Mean	ND	ND	ND	ND	2.80
	CV%					15.4
f_D (%)	Geo Mean	ND	ND	ND	ND	1.20
	CV%					32.1

CV% geometric coefficient of variation; Geo Mean geometric mean; n number of subjects; ND not determined.
[a] protocol-correct subjects
[b] all subjects
[c] Subjects received a single 25-mg NKTR-118 dose 2 hours before start of hemodialysis session.

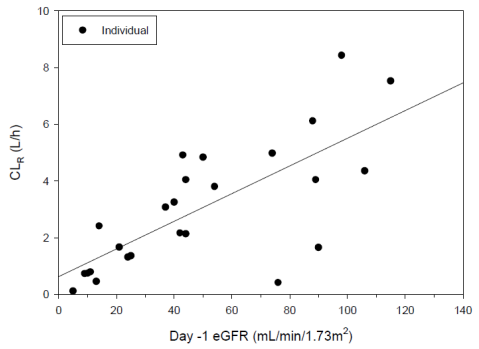
Table 11.2.4.2 Summary of amount (ng) and fraction of dose (%) excreted in urine as NKTR-118 cumulatively by collection interval for per-protocol subjects based on MDRD formula (Pharmacokinetic analysis set)

Renal group/ Period [a]	Summary statistic	Cumulative amount excreted (ng)				Cumulative fraction of dose excreted (%)			
		0-12h	0-24h	0-48h	0-72h	0-12h	0-24h	0-48h	0-72h
Normal (N=6) [b]	n	6	6	6	6	6	6	6	6
	Geometric mean	1180000	1300000	1310000	1310000	4.71	5.20	5.22	5.22
	CV%	71.3	65.5	66.1	66.1	71.2	65.3	66.0	66.0
	Arithmetic mean	1360000	1480000	1490000	1490000	5.45	5.93	5.97	5.97
	SD	688000	739000	751000	751000	2.75	2.96	3.01	3.01
	Median	1400000	1500000	1500000	1500000	5.58	5.97	5.97	5.97
	Minimum	397000	501000	501000	501000	1.59	2.01	2.01	2.01
	Maximum	2060000	2280000	2280000	2280000	8.24	9.13	9.13	9.13
Moderate (N=8)	n	8	8	8	8	8	8	8	8
	Geometric mean	1190000	1480000	1590000	1610000	4.76	5.92	6.36	6.43
	CV%	41.3	47.3	52.3	53.6	41.3	47.3	52.3	53.6
	Arithmetic mean	1270000	1600000	1740000	1770000	5.07	6.39	6.97	7.09
	SD	462000	609000	715000	748000	1.85	2.43	2.86	2.99
	Median	1310000	1600000	1650000	1650000	5.22	6.38	6.60	6.60
	Minimum	587000	593000	593000	593000	2.35	2.37	2.37	2.37
	Maximum	2060000	2450000	2750000	2820000	8.24	9.81	11.0	11.3
Severe (N=8)	n	8	8	8	8	8	8	8	8
	Geometric mean	524000	591000	601000	601000	2.09	2.36	2.40	2.40
	CV%	89.3	101.2	104.0	104.0	89.1	100.9	103.8	103.8
	Arithmetic mean	716000	852000	879000	879000	2.86	3.40	3.51	3.51
	SD	751000	949000	1010000	1010000	2.99	3.78	4.02	4.02
	Median	455000	527000	552000	552000	1.82	2.10	2.20	2.20
	Minimum	236000	236000	236000	236000	0.944	0.944	0.944	0.944
	Maximum	2510000	3110000	3280000	3280000	10.0	12.4	13.1	13.1

Table 11.2.4.3 Summary of amount (ng) and fraction of dose (%) excreted in urine as NKTR-118 cumulatively by collection interval for each group classified based on Cockcroft-Gault equation (Pharmacokinetic analysis set)

Renal group/ Period [a]	Summary statistic	Cumulative amount excreted (ng)				Cumulative fraction of dose excreted (%)			
		0-12h	0-24h	0-48h	0-72h	0-12h	0-24h	0-48h	0-72h
Normal (N=9)	n	9	9	9	9	9	9	9	9
	Geometric mean	943000	1060000	1070000	1080000	3.77	4.23	4.30	4.31
	CV%	134.2	141.4	143.9	144.4	134.3	141.3	143.9	144.4
	Arithmetic mean	1260000	1430000	1470000	1470000	5.05	5.74	5.87	5.90
	SD	704000	823000	856000	865000	2.82	3.29	3.43	3.46
	Median	1470000	1570000	1650000	1650000	5.88	6.29	6.59	6.59
	Minimum	92300	92300	92300	92300	0.369	0.369	0.369	0.369
	Maximum	2060000	2360000	2520000	2580000	8.24	9.42	10.1	10.3
Mild (N=3)	n	3	3	3	3	3	3	3	3
	Geometric mean	1190000	1320000	1370000	1380000	4.77	5.27	5.47	5.52
	CV%	71.6	83.2	90.9	92.7	71.5	83.4	91.0	92.9
	Arithmetic mean	1350000	1540000	1640000	1660000	5.40	6.15	6.55	6.65
	SD	738000	929000	1080000	1120000	2.95	3.72	4.32	4.48
	Median	1400000	1570000	1570000	1570000	5.60	6.28	6.28	6.28
	Minimum	587000	593000	593000	593000	2.35	2.37	2.37	2.37
	Maximum	2060000	2450000	2750000	2820000	8.24	9.81	11.0	11.3
Moderate (N=6)	n	6	6	6	6	6	6	6	6
	Geometric mean	1180000	1520000	1630000	1650000	4.73	6.06	6.53	6.58
	CV%	45.9	43.9	47.9	48.6	45.8	43.8	47.8	48.5
	Arithmetic mean	1290000	1640000	1780000	1800000	5.15	6.55	7.13	7.20
	SD	644000	777000	854000	864000	2.56	3.09	3.41	3.45
	Median	1160000	1490000	1570000	1570000	4.62	5.96	6.28	6.28
	Minimum	746000	914000	914000	914000	2.98	3.65	3.65	3.65
	Maximum	2510000	3110000	3280000	3280000	10.0	12.4	13.1	13.1
Severe (N=6)	n	6	6	6	6	6	6	6	6
	Geometric mean	380000	417000	422000	422000	1.52	1.67	1.69	1.69
	CV%	44.7	53.5	55.2	55.2	44.6	53.3	54.9	54.9
	Arithmetic mean	411000	465000	474000	474000	1.64	1.86	1.89	1.89
	SD	184000	247000	255000	255000	0.736	0.984	1.02	1.02
	Median	357000	376000	376000	376000	1.43	1.50	1.50	1.50
	Minimum	236000	236000	236000	236000	0.944	0.944	0.944	0.944
	Maximum	716000	874000	874000	874000	2.86	3.49	3.49	3.49

The following is a plot of the eGFR vs. CLr (L/h) for each individual in this study; While there was a definite trend, data was tighter at the lower end of eGFR (ESRD, severe and moderate impairment), compared to data at the higher range of renal function (mild to normal):



Statistical comparisons: poor correlation was noted between exposure and eGFR. Geometric LS mean ratios (vs. normal) and 90 % CI surrounding the ratio are provided as further means of comparing data:

				Comparison to normal renal function group	
Parameter	**Renal Group[a]**	**N**	**Geometric LS mean**	**Ratio (%)**	**90% CI**
AUC	Normal	6	281.4		
(ng*h/mL)	Moderate	8	487.1	173.06	(101.20, 295.94)
	Severe	8	611.8	217.39	(127.12, 371.76)
	ESRD	8	270.1	95.98	(56.12, 164.13)
C_{max}	Normal	6	80.54		
(ng/mL)	Moderate	8	89.43	111.04	(71.39, 172.71)
	Severe	8	148.2	184.01	(118.31, 286.20)
	ESRD	8	57.18	70.99	(45.64, 110.41)

Data suggests that AUC was higher in both moderate and severe renal impairment subjects compared to normal subjects; In the severe RI group, the 90 % CI bounds were completely outside the 80-125 % standard bounds. In the ESRD patients, while the treatment mean ratio for AUC was close to unity, the lower confidence bound was much below the standard 80 % lower limit. Note that the study was not powered to establish statistically significant differences.

When compared to subjects with normal renal function, geometric LS mean AUC and Cmax values were 73% and 11% higher in subjects with moderate renal impairment, respectively. Similarly, when compared to normal renal function, geometric LS mean AUC and Cmax values were 117% and 84% higher in subjects with severe renal impairment, respectively. Overall exposure of NKTR-118 in ESRD subjects appeared to be similar to that for normal renal function while maximum exposure was 29% lower compared to subjects with normal renal function.

Data comparing pre- and post-hemodialysis naloxegol suggest comparable LS mean ratios, with the 90 % confidence bounds for AUC falling within the 80-125 % bounds, while Cmax bounds fell outside the upper bound as shown:

Parameter	Renal Group[a]	N	Geometric LS mean	Ratio (%)	Pairwise comparison Pre-HD/Post-HD 90% CI
AUC	Post-HD	8	270.1		
(ng*h/mL)	Pre-HD	8	281.6	104.24	(92.40, 117.59)
C_{max}	Post-HD	8	57.18		
(ng/mL)	Pre-HD	8	66.1	115.61	(90.90, 147.04)

Results based on a paired t-test for posthemodialysis versus prehemodialysis. Only ESRD subjects are included in this analysis. CI confidence interval; LS least squares; Pre-HD prehemodialysis; Post-HD posthemodialysis

Drug is not removed by dialysis as noted by fraction of dose (%) excreted in dialysate:

Table 11.2.5 Summary of amount (ng) and fraction of dose (%) excreted in dialysate as NKTR-118 by collection interval in ESRD subjects
(Pharmacokinetic analysis set)

Renal group/ Period [a]	Summary statistic	Amount excreted (ng) 0-1h	1-2h	2-3h	3-4h	Fraction of dose excreted (%) 0-1h	1-2h	2-3h	3-4h
ESRD (N=8)/P2	n	8	8	8	8	8	8	8	8
	Geometric mean	118000	84300	54000	39700	0.472	0.337	0.216	0.159
	CV%	44.8	35.4	27.7	30.3	44.8	35.4	27.7	30.2
	Arithmetic mean	128000	88800	55900	41200	0.513	0.355	0.223	0.165
	SD	59300	31000	16600	12500	0.237	0.124	0.0662	0.0500
	Median	112000	84800	50300	41100	0.448	0.339	0.201	0.164
	Minimum	65600	55900	39000	28300	0.262	0.224	0.156	0.113
	Maximum	245000	144000	89600	64300	0.980	0.576	0.358	0.257

NKTR-118 - Study D3820C00009

Table 11.2.6 Summary of amount (ng) and fraction of dose (%) excreted in dialysate as NKTR-118 cumulatively by collection interval in ESRD subjects (Pharmacokinetic analysis set)

Renal group/ Period [a]	Summary statistic	Cumulative amount excreted (ng) 0-1h	0-2h	0-3h	0-4h	Cumulative fraction of dose excreted (%) 0-1h	0-2h	0-3h	0-4h
ESRD (N=8)/P2	n	8	8	8	8	8	8	8	8
	Geometric mean	118000	204000	259000	300000	0.472	0.818	1.04	1.20
	CV%	44.8	37.7	34.0	32.1	44.8	37.9	33.9	32.1
	Arithmetic mean	128000	217000	273000	314000	0.513	0.869	1.09	1.26
	SD	59300	85600	100000	110000	0.237	0.344	0.400	0.440
	Median	112000	196000	249000	283000	0.448	0.785	0.996	1.13
	Minimum	65600	124000	178000	214000	0.262	0.494	0.713	0.858
	Maximum	245000	389000	479000	543000	0.980	1.56	1.91	2.17

Four subjects in the severe group actually had a eGFR < 15 thus rendering them ESRD not yet on hemodialysis; the table below summarizes exposures and fold changes in ESRD, ESRD post-HD, ESRD pre-HD compared to normal; all groups have n = 8 except ESRD (not yet on dialysis) which has n =4:

					Fold Change Relative to Normal		
PK	Normal	ESRD	ESRD Post-HD	ESRD Pre-HD	ESRD	Post-HD	Pre-HD
Cmax	83 ± 44	166 ± 59	63 ± 29	71 ± 30	2.00	0.76	0.86
AUCt	213 ± 48	691 ± 577	283 ± 95	292 ± 96	3.24	1.33	1.37

It appears that ESRD patients who are not yet on dialysis (based on a small N = 4), have approximately 2-fold and 3-fold higher Cmax and AUC compared to control group; however, the variability was large in the small ESRD group; In comparison, ESRD patients on dialysis had lower exposures;

Safety information for subjects with high exposures: Subjects 1003 had documented mild hyperglycemia which is noted to have started 33 h after dose; Subject 1005 experienced a fatal myocardial infarction 17 days after receiving a dose of NKTR-118, which was deemed unrelated to study drug due to prior history of congestive heart failure, hypertension, and diabetes. He was found to have multi-vessel coronary artery disease and underwent coronary artery bypass graft surgery on Day 25. He died of sudden cardiac death on Day 35. The event was assessed by the Investigator as not related to IP. There are no reported AEs for subject 1020 (highest exposure) and subject 2013.

Discussion and Conclusions: The f_e for naloxegol is ~ 10 %. Thus renal clearance seems to be a minor pathway. Naloxegol has very low PPB (~ 4 %), thus it is acceptable that sponsor did not evaluate unbound drug concentrations in this study. In this study, per sponsor's original grouping of the renal subjects, an average of 73 % and 117 % increase in AUC was noted in subjects with moderate and severe renal impairment, respectively compared to normal subjects; In addition the Cmax was increased by 84 % in severe RI patients. Averages were primarily driven by two individuals each in the moderate and severe subgroups, while the remaining individuals had exposures comparable to the control group. Clinical characteristics of the individuals with markedly higher exposures were comparable to other study participants. ESRD patients on dialysis had systemic exposures comparable to those in normal subjects when dosed 1 to 2 hours before or after hemodialysis.

Four subjects in the severe group (MDRD) actually had eGFR < 15, thus fitting the criteria for ESRD not yet on dialysis; Thus data table below summarizes PK parameters per that definition:

	Normal	Moderate	Severe	ESRD	ESRD Post-HD	ESRD Pre-HD
	N = 8	N= 8	N = 4	N = 4	N = 8	N = 8
Cmax	83 ± 44	94 ± 38	186 ± 177	166 ± 59	63 ± 29	71 ± 30
AUCt	299 ± 113	577 ± 394	953 ± 1051	691 ± 577	283 ± 95	292 ± 96
CL/F	93 ± 34	60 ± 33	49 ± 31	51 ± 26	100 ± 46	93 ± 93
T1/2	11.8 ± 7.9	11.9 ± 5.4	11.8 ± 5.2	12.8 ± 11.2	11.4 ± 7.3	9.2 ± 4.5
Vz/F	1414 ± 791	1137 ± 1296	704 ± 372	841 ± 972	1523 ± 942	1196 ± 674

Fold change vs. normal	Mod	Severe	ESRD	Post-HD	Pre-HD
	N= 8	N = 4	N = 4	N = 8	N = 8
Cmax	1.13	2.24	2.00	0.76	0.86
AUC0-t	1.93	3.18	2.3	0.94	0.97
CL/F	0.65	0.53	0.54	1.07	1.00
T1/2	1.01	1.00	1.08	1.08	0.78
Vz/F	0.80	0.50	0.59	1.07	0.85

Thus when categorized by the renal function grouping recommended by the revised 2010 guidance, it appears that the arithmetic Cmax averages were higher in moderate, severe and ESRD (not on dialysis) groups by 1.13-, 2.24- and 2.00 fold, respectively compared to normal subjects, while the AUC values were higher by 1.93, 3.18, and 2.3-fold compared to normals.

A statistical comparison (bioequivalence analysis) of various RI groups versus normal (reference) is summarized below (Phoenix):

Ratio (%)	Moderate	Severe	ESRD	ESRD Post-HD; (n = 8)	ESRD Pre-HD; (n = 8)

90 % CI	(n = 8)	(n = 4)	(n = 4)		
Cmax	118.09 [81 – 175]	186.79 [116- 301]	207.86 [129 – 335]	89.01 [60 – 131]	75.05 [51- 111]
AUCt	170.77 [108-268]	230.99 [132-401]	198.27 [114-344]	94.50 [60 – 148]	98.50 [63 – 155]

Analysis using geometric mean data suggests that compared to normal subjects, patients with moderate, severe and ESRD (not on dialysis) had ~ 18 %, 86 % and 107 % higher Cmax and ~ 70 %, 131 %, and 98 % higher AUC;

Additional analysis: Based on fold-change data below (using MDRD or Clcr based classification) after removing the four 'outliers', it appears that fold increases in exposure in severe renal impairment patients were ~40- 50 % higher, while in moderate RI patients ~ 10-33 % increase was noted for Cmax & AUC;

PK without the outliers (Subjects 1003, 1005, 2013 and 1020); MDRD

				Fold Change vs. normal	
	Normal	Moderate	Severe	Moderate	Severe
Cmax (ng/mL)	82.99	80.33	122.87	0.97	1.48
AUC (ng.h/mL)	301.88	377.17	424.00	1.25	1.40
CL/F (L/h)	92.93	72.55	62.33	0.78	0.67

PK without the outliers (Subjects 1003, 1005, 2013, 1020); CG

					Fold Change vs. normal		
	Normal	Mild	Moderate	Severe	Mild	Moderate	Severe
Cmax (ng/mL)	82.99	79.1	90.95	123.44	0.95	1.10	1.49
AUC (ng.h/mL)	301.88	266.50	400.75	427.00	0.88	1.33	1.41
CL/F (L/h)	92.93	99.75	62.58	62.56	1.07	0.67	0.67

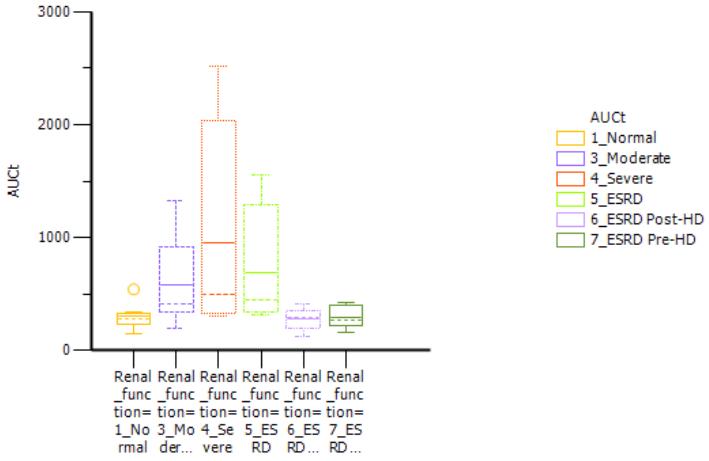
MDRD without outliers (all groups); exposures only

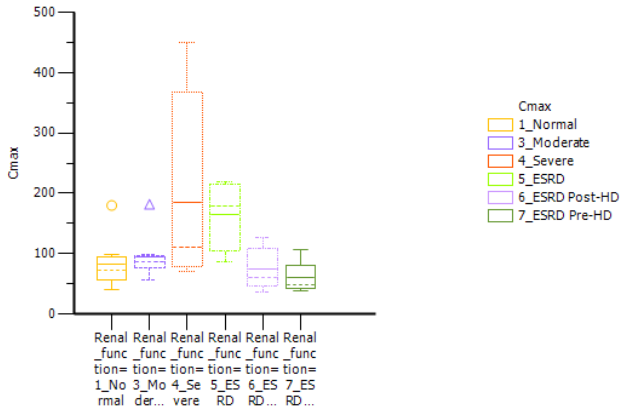
	Normal	Moderate	Severe	ESRD	Post-HD	Pre-HD
Cmax (ng/mL)	82.99	80.33	97.73	148.00	62.68	71.18
AUC (ng.h/mL)	301.88	373.67	430.67	405.67	283.63	292.13

	Fold Change vs. normal				
	Moderate	Severe	ESRD	Post-HD	Pre-HD
Cmax	0.97	1.18	1.18	0.76	0.86
AUCt	1.24	1.43	1.34	0.94	0.97

Sponsor has not proposed dose adjustments based on renal function category; (b) (4)

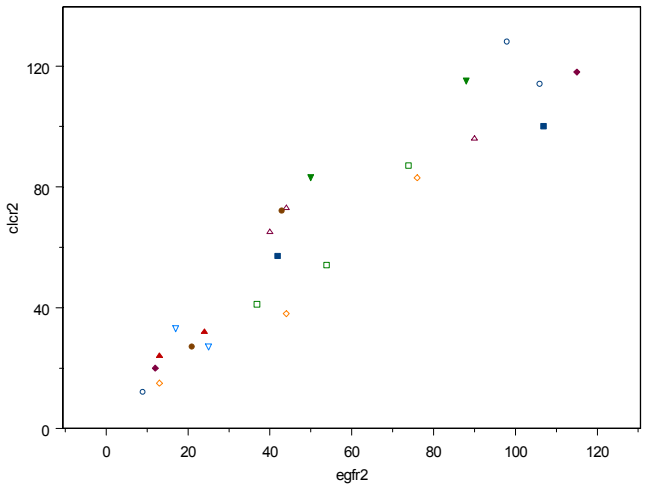
Although the mean increases in Cmax and AUC were at the most 2 – 2.3 fold, the individuals (n = 4) experienced a maximum Cmax and AUC increases of 5-fold and 8.4 fold (maximum of the range noted). While there was no apparent correlation of eGFR and exposures, one cannot rule out an impact of impaired renal function on metabolic and/or transporter function at gut or liver leading to increased exposures, especially in patients with more severe renal disease. One cannot at this point rule out greater susceptibility in some individuals with severe renal disease. Thus a lower initial dose of 12.5 mg could be considered in patients with greater than mild renal impairment with the option of increasing dose if efficacy is found inadequate; In clinical trials of naloxegol 12.5 mg dose was efficacious (statistically significant in only one of the two trials); additional covariate analyses from Pharmacometrics review should also be considered prior to making final decision in this regard.

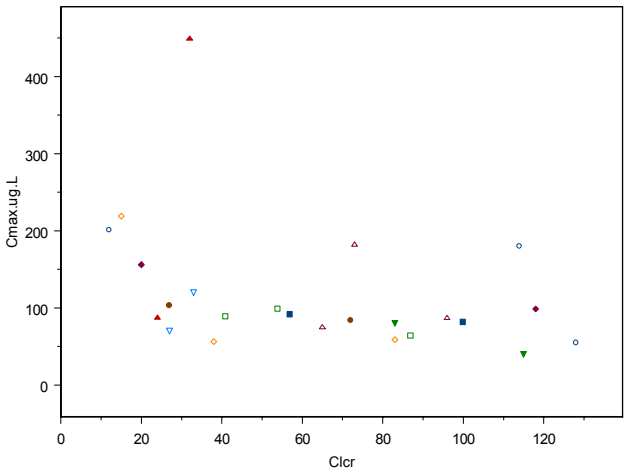


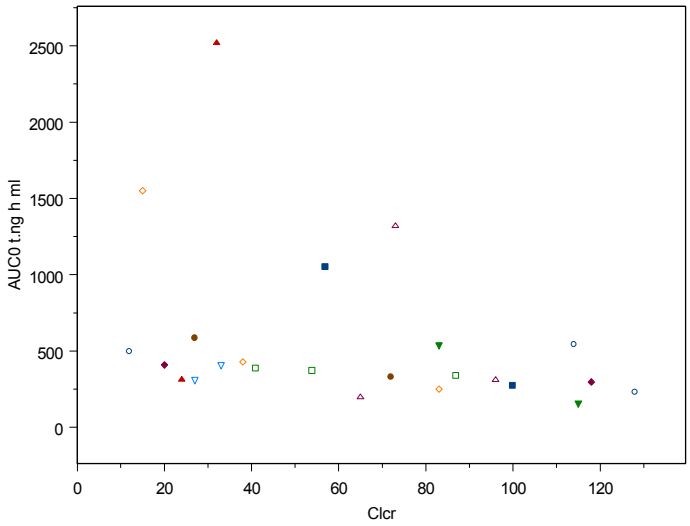


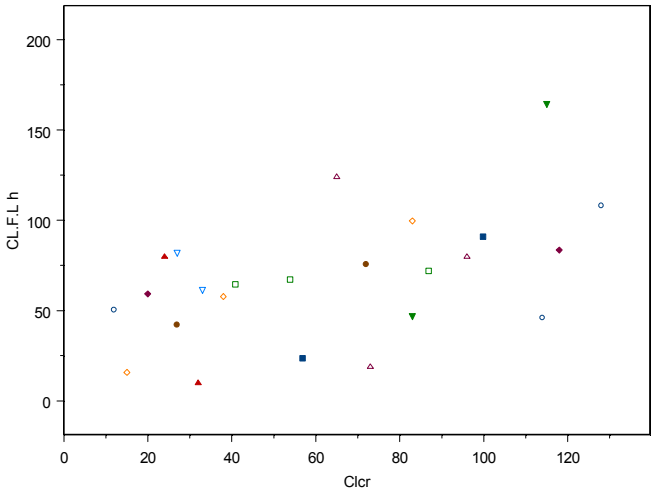
Mean (SD); [Range]	Normal (n = 8)	Moderate (n =8)	Severe (n = 4)	ESRD (n = 4)	ESRD Post-HD Dose (n = 8)	ESRD; Pre-HD Dose (n = 8)
Cmax (ng/mL)	83 (44); [40 -180]	94 (38); [56 – 182]	186 (176); [70 – 449]	166 (59); [87 – 219]	63 (31); [36 – 127]	71 (30); [42 – 115]
AUCt (ng.h/mL)	299 (114); [152-542]	576 (394); [197-1320]	953 (1051); [305-2520]	692 (577); [313-1550]	284 (95); [126 – 413]	292 (97); [161- 429]
CL/F (L/h)	93 (34); [46 – 164]	60 (33); [19 – 124]	49 (31); [10 – 82]	51 (27); [16 – 80]	100 (46); [60 – 197]	93 (32); [58 – 153]
Vz/F (L)	1414 (791); [797–3110]	1137(1296) [384-4300]	705 (372); [196-1090]	842 (972); [340-2300]	1523(941); [559-2860]	1195(674); [600-2750]

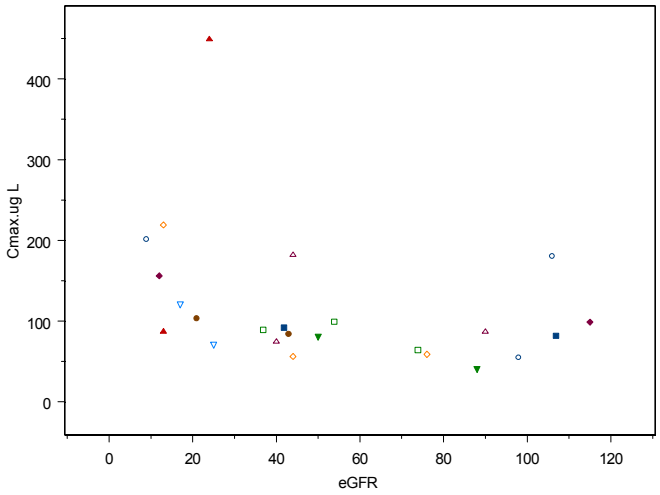
Reviewer's plots with renal function as a continuous variable:

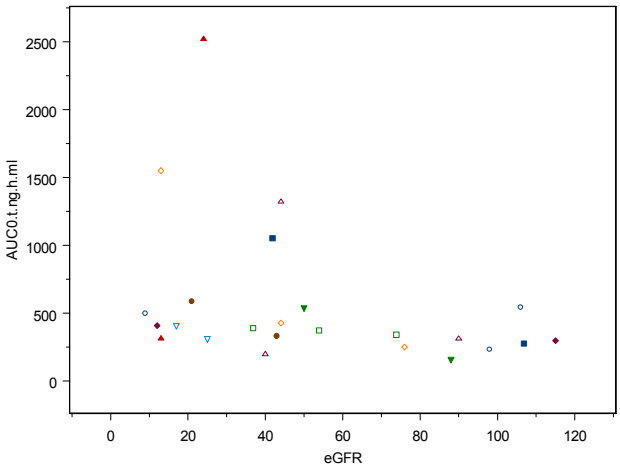

clcr2
egfr2
0
40
80
120
0
20
40
60
80
100
120

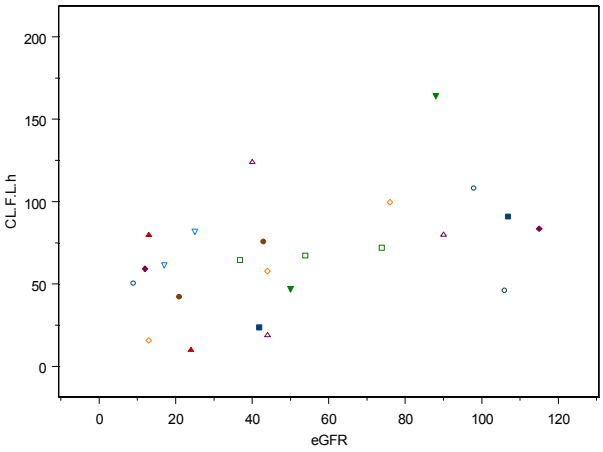

Cmax.ug.L
Clcr
0
100
200
300
400
0
20
40
60
80
100
120

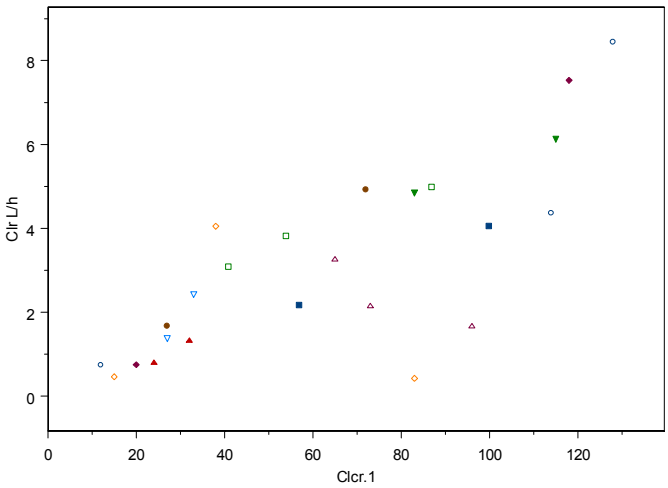


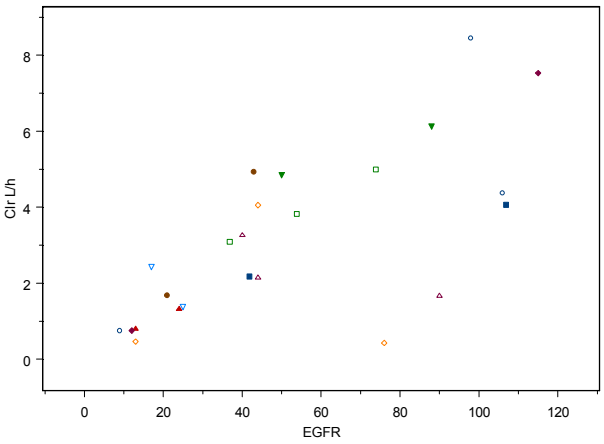



Cmax.ug.L
400
300
200
100
0
0
20
40
60
80
100
120
eGFR


AUC0.t.ng.h.ml
2500
2000
1500
1000
500
0
0
20
40
60
80
100
120
eGFR


CL.F.L.h
200
150
100
50
0
0
20
40
60
80
100
120
eGFR


Clr L/h
8
6
4
2
0
0
20
40
60
80
100
120
Clcr.1


Clr L/h
8
6
4
2
0
0
20
40
60
80
100
120
EGFR

*** Linear Model ***

Call: lm(formula = **Cmax.ug.L ~ eGFR**, data = SDF88, na.action = na.exclude)
Residuals:
   Min   1Q Median   3Q   Max
 -70.79 -41.72 -31.23 17.91 307.1

Coefficients:
             Value Std. Error   t value Pr(>|t|)
(Intercept) 162.7680   30.9832   5.2534   0.0000
      eGFR   -0.8711   0.5032   -1.7310   0.0974

Residual standard error: 82.23 on 22 degrees of freedom
Multiple R-Squared: 0.1199   Adjusted R-squared: 0.07987
F-statistic: 2.996 on 1 and 22 degrees of freedom, the **p-value is 0.09745**
29 observations deleted due to missing values

*** Linear Model ***

Call: lm(formula = **AUC0.t.ng.h.ml ~ eGFR**, data = SDF88, na.action = na.exclude)
Residuals:
  Min   1Q Median   3Q Max
 -470 -291.8 -167.7 34.3 1799

Coefficients:
             Value Std. Error   t value Pr(>|t|)
(Intercept) 855.7539 194.8666   4.3915   0.0002
      eGFR   -5.5991   3.1651   -1.7690   0.0908

Residual standard error: 517.2 on 22 degrees of freedom
Multiple R-Squared: 0.1245   Adjusted R-squared: 0.08474
F-statistic: 3.129 on 1 and 22 degrees of freedom, the **p-value is 0.09075**
29 observations deleted due to missing values

*** Linear Model ***

Call: lm(formula = **CL.F.L.h ~ eGFR**, data = SDF88, na.action = na.exclude)
Residuals:
   Min   1Q Median   3Q   Max
 -47.83 -15.93 -2.512 13.68 78.97

Coefficients:
             Value Std. Error t value Pr(>|t|)
(Intercept) 42.5362 12.1000   3.5154 0.0020
      eGFR 0.4829 0.1965   2.4573 0.0224

Residual standard error: 32.11 on 22 degrees of freedom
Multiple R-Squared: 0.2154   Adjusted R-squared: 0.1797
F-statistic: 6.038 on 1 and 22 degrees of freedom, the **p-value is 0.02235**
29 observations deleted due to missing values

*** Linear Model ***

Call: lm(formula = **Clr.L.h ~ Clcr.1**, data = SDF88, na.action = na.exclude)
Residuals:
    Min   1Q Median   3Q   Max
 -3.656 -0.5506 0.01661 0.8171 2.246

Coefficients:
             Value Std. Error t value Pr(>|t|)
(Intercept) 0.1722 0.6031   0.2854 0.7780
    Clcr.1 0.0470 0.0083   5.6524 0.0000

Residual standard error: 1.454 on 22 degrees of freedom

Multiple R-Squared: 0.5922 Adjusted R-squared: 0.5737
F-statistic: 31.95 on 1 and 22 degrees of freedom, the **p-value is 0.00001103**
36 observations deleted due to missing values

*** Linear Model ***

Call: lm(formula = **Clr.L.h ~ EGFR**, data = SDF88, na.action = na.exclude)
Residuals:
Min 1Q Median 3Q Max
-3.826 -0.5941 -0.2577 0.9655 3.189

Coefficients:
Value Std. Error t value Pr(>|t|)
(Intercept) 0.7781 0.6143 1.2667 0.2185
EGFR 0.0456 0.0100 4.5743 0.0001

Residual standard error: 1.63 on 22 degrees of freedom
Multiple R-Squared: 0.4875 Adjusted R-squared: 0.4642
F-statistic: 20.92 on 1 and 22 degrees of freedom, the **p-value is 0.0001484**
36 observations deleted due to missing values

D3820C00010- An Open-label, Single Center Study to Assess the Pharmacokinetics of NKTR-118 in Patients with Impaired Hepatic Function and Healthy Volunteers with Normal Hepatic Function Following Administration of a Single Dose of 25 mg NKTR-118 [Naloxegol]

Background: NKTR-118 is a polyethylene glycol-ylated (PEG-ylated) derivative of naloxone, currently under investigation for treatment of opioid-induced constipation (OIC). Preclinical data suggest that biliary excretion and hepatic metabolism may play an important role in NKTR-118 elimination. Furthermore, in an absorption, distribution, metabolism, and excretion (ADME) study, approximately 84% of the orally administered dose of radioactivity was recovered, with approximately 16 % eliminated in urine and approximately 68% eliminated in feces. The current study was conducted to gain a better understanding of the relationship between hepatic impairment and the exposure, to investigate safety and tolerability, and to provide dosing recommendations for such populations, if appropriate.

Study Objectives:

Primary: To assess the PK of a single oral dose of 25 mg NKTR-118 in patients with impaired hepatic function (mild and moderate) compared to that in healthy volunteers with normal hepatic function

Secondary: To examine the safety and tolerability of a single oral dose of 25 mg NKTR-118 in patients with impaired hepatic function and in healthy volunteers with normal hepatic function.

Study design: A single dose, nonrandomized, open-label, parallel group study in a total of 24 subjects (3 groups of 8 each) with normal hepatic function, and mild (C-P A) or moderate (C-P B) HI. Hepatic impairment was assessed based on the patients' Child-Pugh classification.

Use of medications which prolong the QT interval and/or were strong inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (PGP) were part of study exclusions. Other exclusions included any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 72 hours of the investigational product administration. Also excluded were subjects with moderate or severe renal dysfunction according to age-related creatinine clearance estimated using the method of Cockcroft and Gault (ie, creatinine clearance less than 50 mL/min).

Study period: After the initial screening visit, each subject remained resident in the clinic from day -1 until day 6. A follow up visit occurred 7-10 days after discharge. C-P classification was obtained at screening and again on day -1 if screening was more than one week prior to day -1. Naloxegol was administered on the morning of day 1. PK sampling occurred on days 1 to 6. Blood samples for pharmacokinetic analysis were collected before administration of NKTR-118 and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 hours post-dose. The sequence of assessments at a particular time point was: 1) electrocardiogram (ECG), 2) blood pressure and pulse rate, 3) PK sample collection.

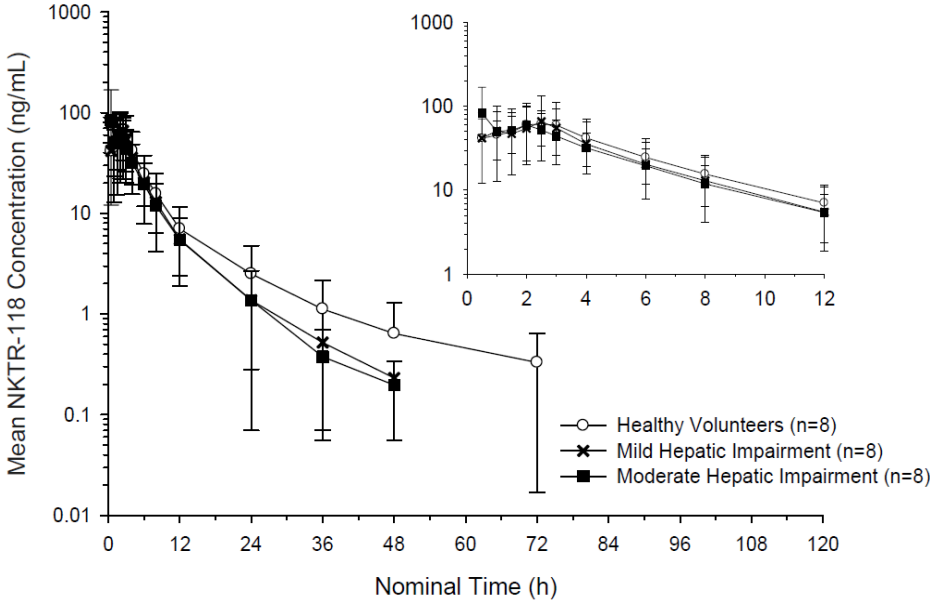
Sponsor notes the following: "Patients with severe hepatic impairment were not included in this study as the degree of hepatic impairment and resultant potential effects on most opioid metabolism as well as associated symptoms, such as encephalopathy, would be a relative contraindication for most hepatic impairment patients to receive opioids. Subsequently, they are unlikely to have a need for treatment with NKTR-118".

Results:

The concentrations of NKTR_118 in human plasma were determined by solid phase extraction and liquid chromatography followed by tandem mass spectrometric detection (LC-MS/MS) according to Method NKTHPP. The analytical method has a calibration range of 0.100 ng/mL to 50.0 ng/mL, utilizing a 0.100 mL sample aliquot,

with a validated dilution of 100-fold with human plasma. The calibration curve data, QC sample data, and the ISR results from the Bioanalytical report appear to have met the acceptance criteria. The precision (%CV) and accuracy (% bias) for the QC samples at 3 concentrations were ≤3.9% and were within -2.0% to -0.8%, respectively, which indicated that the method performed reliably during the analysis of study samples. All study samples were analyzed within the (386 days) established stability for NKTR_118 in human plasma. QC samples represented the range of the samples analyzed.

The mean (±SD) NKTR-118 plasma concentration-time profiles for patients with hepatic impairment and for healthy volunteers with normal hepatic function following single administration of NKTR-118 25 mg white film-coated tablet in a fasted state are presented in the figure below:



Summary of arithmetic mean PK parameters by hepatic impairment (C-P) classification:

Mean ± SD	Normal (n = 8)	Mild HI (n = 8)	Moderate HI (n = 8)
Cmax (ng/mL)	84 ± 32	82 ± 40	97 ± 77
Tmax Median [Range]	2.0 [0.5-3.0]	2.25 [0.5 -3.0]	0.55 [0.5 – 2.5]
AUC24 (ng h/mL)	402 ± 173	357 ± 171	356 ± 204
AUC0-t (ng h/mL)	450 ± 209	375 ± 185	369 ± 215
AUCinf (ng h/mL)	453 ± 211	378 ± 186	372 ± 216
CL/F (L/h)	69 ± 37	85 ± 51	81 ± 29

Vz/F (L)	1155 ± 655	1265 ± 1073	873 ± 359
T1/2 (h)	13.1 ± 7.5	13.1 ± 14.6	8.2 ± 3.6

Median Tmax (time to peak plasma concentrations) appeared faster in moderate HI group. Average clearance (CL/F) values in the mild and moderate HI groups were greater compared to normal subjects; T1/2 value appeared smaller in moderate hepatic impairment. Exposure changes for Cmax suggest higher values in moderate HI, while AUC values in both HI groups were somewhat smaller compared to normal volunteers. Volume of distribution was smaller in moderate HI.

Sponsor has provided the following individual plasma concentration-time profiles grouped by hepatic function:

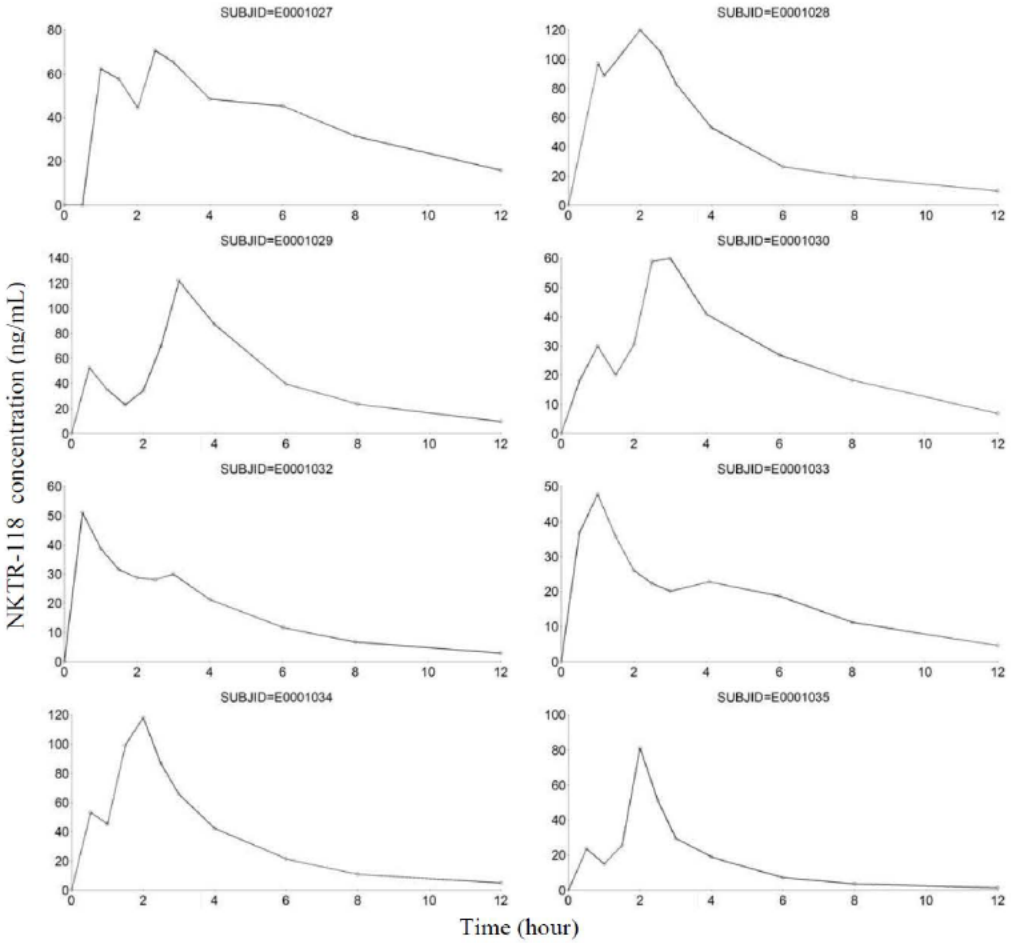
Double peaks were noted in all normal subjects, with the second peak more prominent than the first peak in 6 out of 8 individuals.

Double peaks were noted in 6/8 mild HI subjects, with the second peak more prominent than the first peak in 4 out of 6 such individuals.

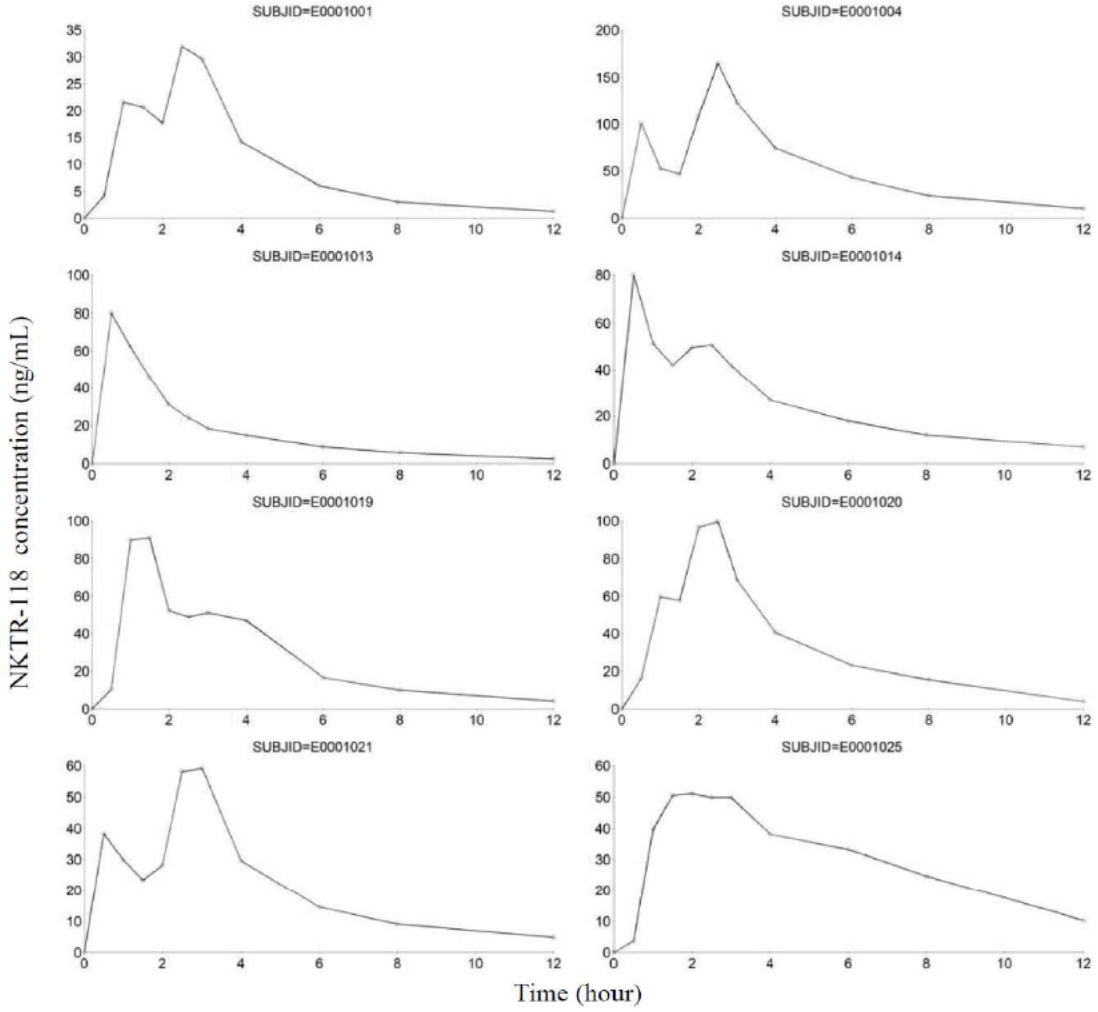
Double peaks were noted in 6/8 moderate HI subjects, with the second peak more prominent than the first peak in only 2 out of 6 such individuals.

Sponsor notes that the enterohepatic recirculation subsequent to biliary excretion (as indicated by the presence of double peaks) appears to be occurring at a lesser degree in patients with moderate hepatic impairment.

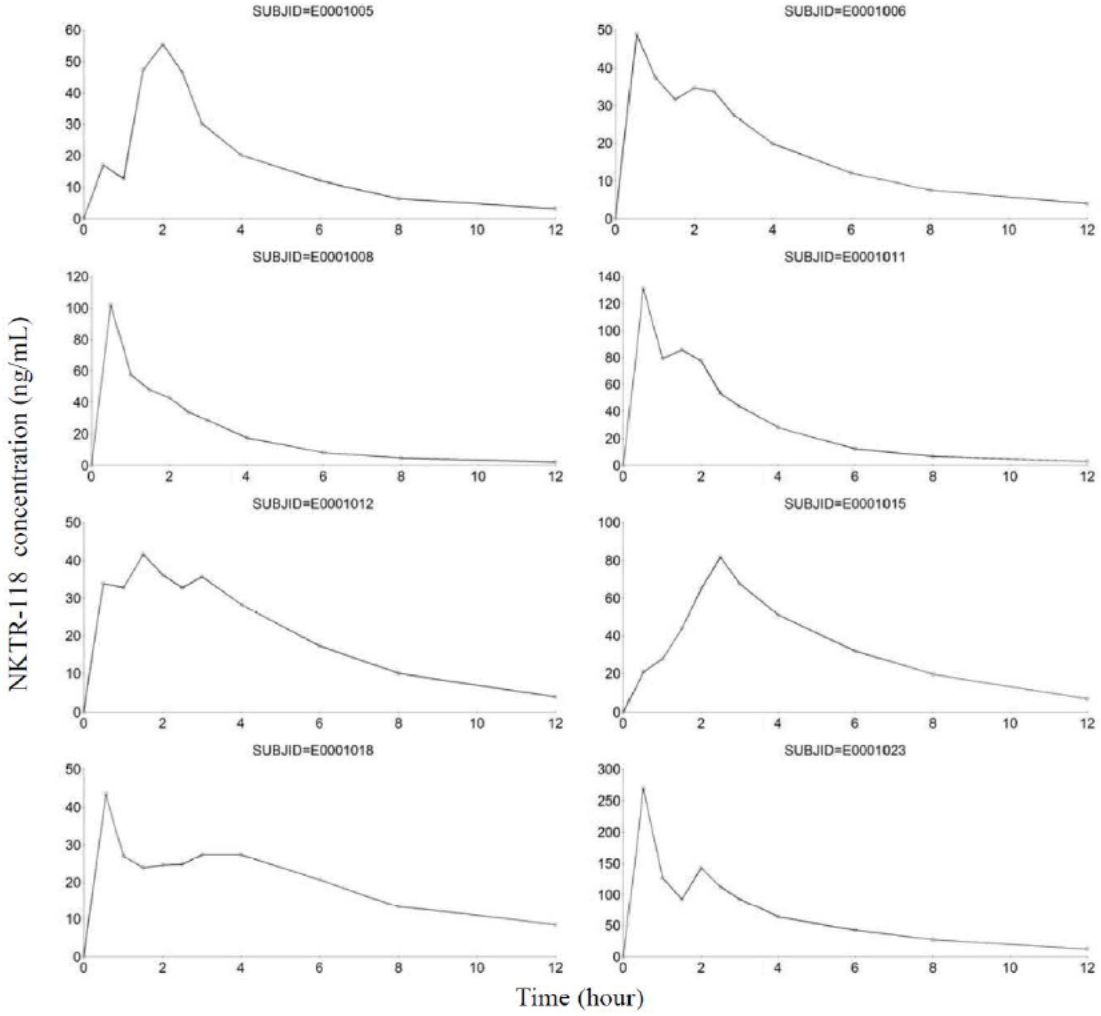
A. Healthy volunteers

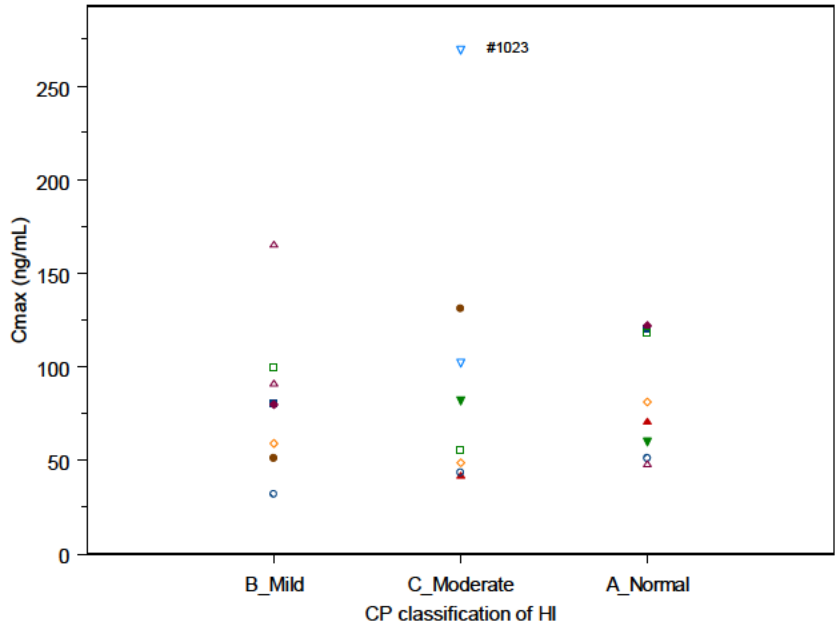


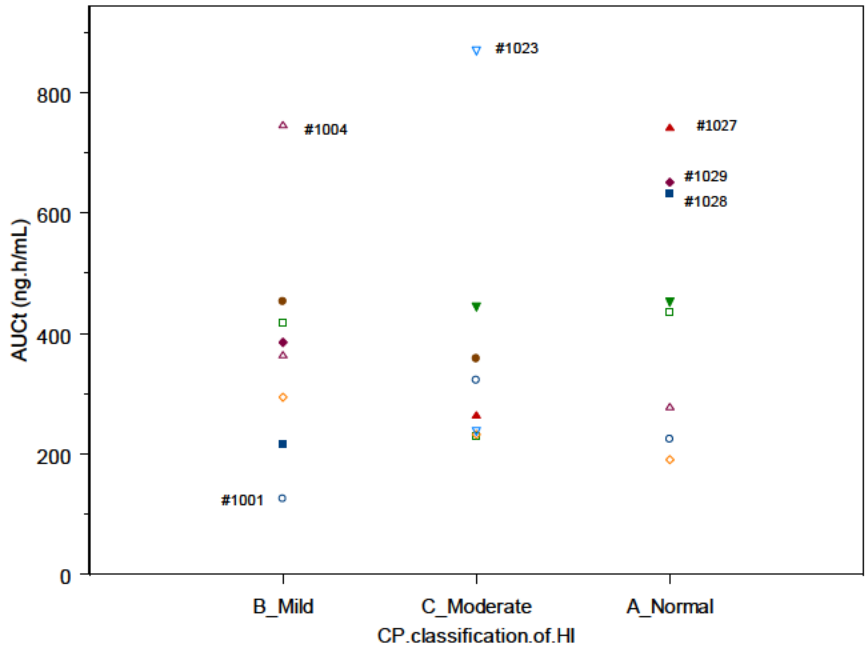
B. Patients with mild hepatic impairment



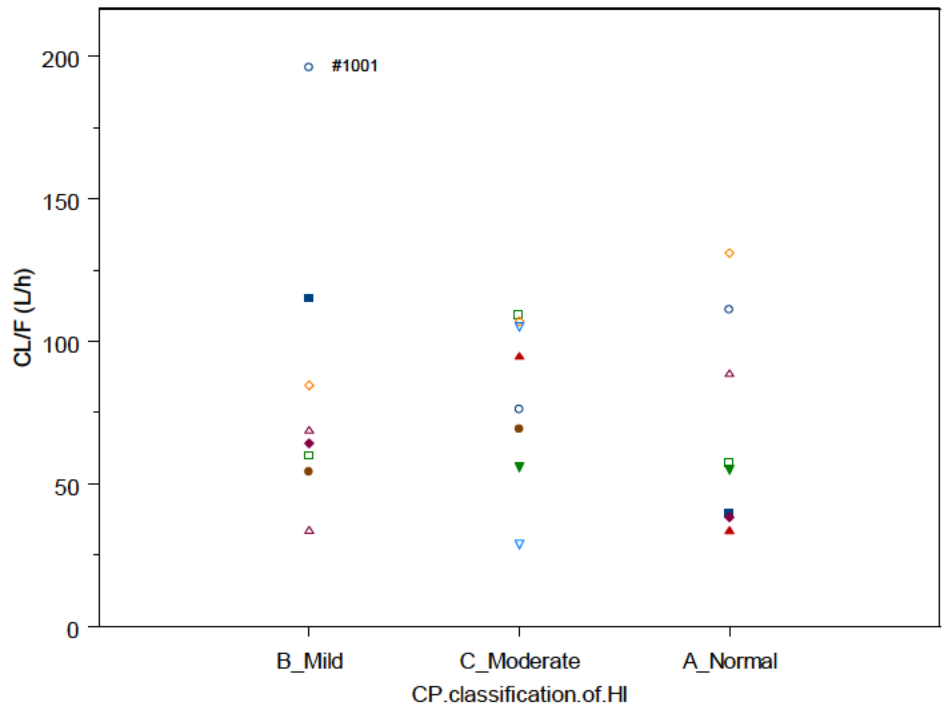
C. Patients with moderate hepatic impairment







Scatter plots for Cmax and AUC parameters suggest that there were one individual each in mild (# 1004) and moderate (#1023) hepatic impairment who had higher exposures compared to others in the group. Although there were no outliers for Cmax in the normal group, AUC was markedly higher for three individuals (# 1027, #1028, #1029) even in the normal group.



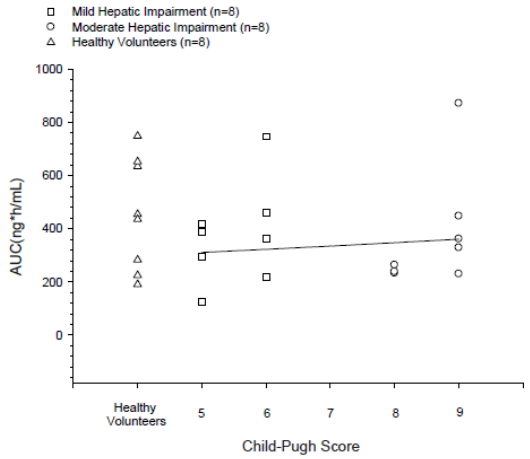
The following table provides the concomitant medications for subjects with higher Cmax and/or AUC values in this study in all three groups; conmeds in #1023 did not suggest causality re:DDI.

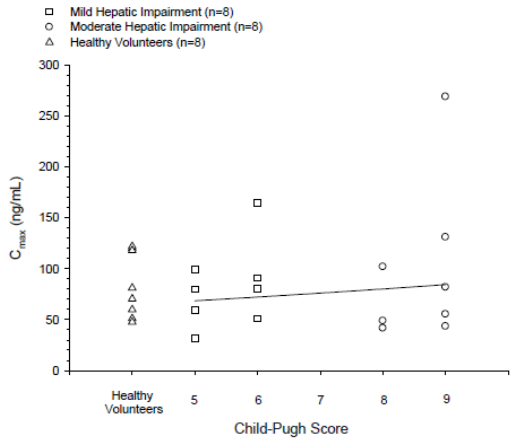
	# 1004 (mild)	# 1023 (moderate)	# 1027 (normal)	# 1028 (normal)	# 1029 (normal)
High Exposures noted	Cmax: 165 ng/mL AUCt: 745 ng.h/mL	Cmax: 269 ng/mL AUCt: 869 ng h/mL	AUCt: 741 ng.h/mL	AUCt: 632 ng.h/mL	AUCt: 651 ng.h/mL
Concomitant diseases/conditions		Chronic back pain, hepatic encephalopathy, hypertension, type II diabetes, GERD, insomnia, hypertension ascites			
	None documented	Diphenhydramine 25mg; Buproprion 150 mg; Cyclobenzaprine 10	None documented	None documented	None documented

		mg prn; Hydrocodone+ paracetamol ? mg; PRN; Lactulose 10 mL TID; Losartan 50 mg Once; Multivitamins 1 tab p.rn; Insulin 20 U s.c., BID; Omeprazole 20 mg PRN Oxycodone + Paracetamol 5 mg PRN; Temazepam 15 mg PRN; Hydrochlorothiazide ?			

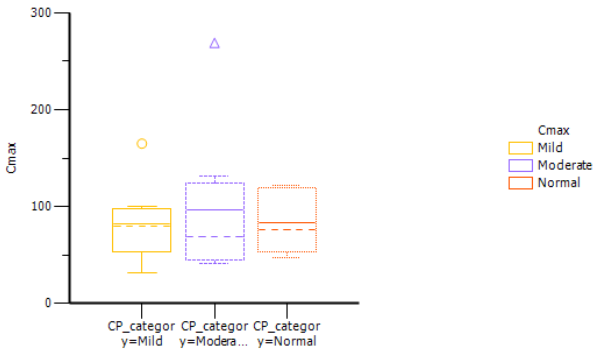
As an exploratory analysis, the relationship between Child-Pugh score in subjects with hepatic impairment and AUC and Cmax was analyzed by the sponsor using a regression model with the Child-Pugh score as a dependent variable and the logarithm of AUC or Cmax as the independent variable. No correlation was noted between C-P scores and exposures:

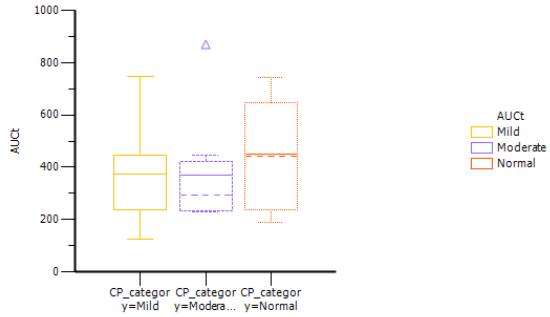
Linear regression of AUC and Cmax versus Child-Pugh score:

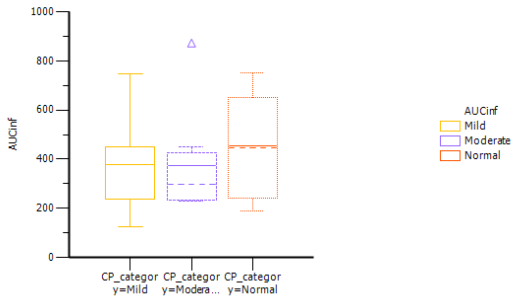




Phoenix WinNonlin was used to generate the following data using PK parameters from the hepatic impairment study:







Summary of bioequivalence type analyses using 'Normal' group as reference is shown below:

Ratio (%) [90 % CI]	Mild HI (n = 8) C-P A (score 5-6)	Moderate HI (n = 8) C-P B (score 7-9)
Cmax	94.55 [60.4 – 147.9]	99.9 [63.8 – 156.4]
AUC0-t	82.80 [53.7 – 127.6]	82.19 [53.4 – 126.7]
AUCinf	82.86 [53.8 – 127.6]	82.27 [53.3 – 126.7]

The geometric mean ratios for Cmax in both mild and moderate HI groups were close to unity relative to normal subjects; for AUC parameters, the ratios suggest somewhat lower exposures in the mild and moderate HI groups compared to normal subjects. The 90 % CI for Cmax and AUC were clearly outside the standard 80- 125 % bioequivalence criteria (exploratory analyses). In the protocol, the sponsor has pre-specified that 'no effect of hepatic impairment on the PK of NKTR-118 was to be indicated if these 90% CIs were completely contained within the 40% limits (60%, 167%)'. No rationale has been provided for this revised criterion.

Overall, AUC values in mild to moderate HI subjects were somewhat lower (16- 17 %) based on geometric mean data, while Cmax data was comparable to normals. Median Tmax was shorter in patients with moderate hepatic impairment, and this may be due to total absence of a secondary peak or only a small secondary peak leading to occurrence of primary peak in the first instance; In normal subjects bimodality was noted, and the secondary peak which usually occurred 1 to 2.5 h after the first peak was usually the largest of the two peaks and thus was deemed the Cmax and its time, as the Tmax for that patient.

Geometric mean apparent terminal half-life (t1/2) for mild and moderate hepatic impairment was shorter (9.64 and 7.54 hours, respectively) than in healthy volunteers (11.3 hours). Sponsor notes that reduced enterohepatic recycling is a potential explanation for the decrease in AUC and t1/2 in hepatic impairment groups.

Nevertheless, data do not indicate that hepatic impairment of mild to moderate category increases the systemic exposures of naloxegol following oral administration of clinically relevant 25 mg single dose. Data from each group included some outliers, including the normal or control group.

Safety: Overall, there was 50 %, 37.5 % and 37.5 % incidence of adverse events in normal, mild HI and moderate HI subjects. No deaths were reported. One serious adverse event (rectal hemorrhage) was noted in subject 1023 in the moderate hepatic impairment group, approximately 8.5 days after the study dose. This subject had the highest Cmax and AUC in this study. Patient had a history of rectal bleeding. The event was considered unrelated to the study drug. One AE of mild hypotension was considered to be related to the investigational product by the investigator. The AE was reported by a patient (# 1018) in the moderate hepatic impairment group. The AE resolved on the same day and lasted one hour.

Conclusions: *It doesn't appear that mild to moderate HI would result in clinically meaningful changes in the systemic exposures of naloxegol and no dosage adjustment would be needed in such patients. Sponsor has not studied patients with severe hepatic impairment, and therefore use in this population is not recommended due to lack of PK and safety information in this regard.*

Note: Hepatic guidance notes the following:

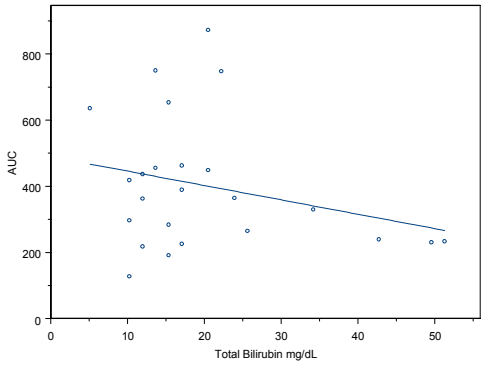
A conclusion that there is no effect (really, no clinically important effect) of hepatic impairment on the drug's PK, would usually be supported by the establishment of one of the following: (1) delineation of no effect boundaries, prior to the conduct of the studies, based on information available for the investigational drug (e.g., dose- and/or concentration-response studies), or (2) in the absence of other information to determine a different equivalence interval, the employment of a standard 90 percent confidence interval of 80-125 percent for AUC and Cmax. FDA recognizes that documentation that a PK parameter remains within an 80-125 percent no effect boundary would be very difficult given the small numbers of subjects usually entered into hepatic impairment studies. If a wider boundary can be supported clinically, however, it may be possible to conclude that there is no need for dose adjustment.

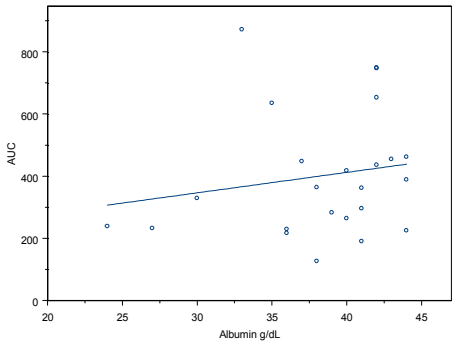
Sponsor noted regarding sample size that 'For indicative purposes, 6 subjects per group will provide >99% power to reject two one-sided null hypothesis that the ratio of geometric means of AUC is outside of the 40% limits (0.6,

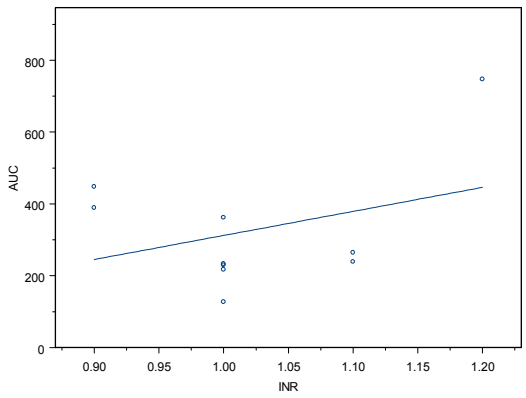
1.67) assuming expected ratio of means is 1.0, coefficient of variation on log scale is 0.14, and the level of significance is 0.05 for each of the tests. The power to reject the null hypothesis that the ratio of geometric means of AUC is outside the 30% limits (0.7, 1.43) is 98% with all other assumptions remaining the same. The coefficient of variation for AUC was referenced from Protocol 08-PNL-04'.

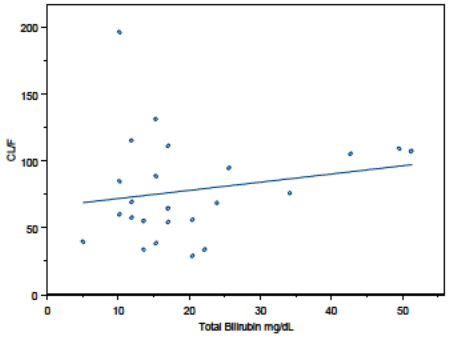
Sponsor pre-specified a 90 % CI of [60 %, 167 %] as the no-effect bounds for this study. Based on this all PK parameters satisfy the upper confidence bound, while only the AUC parameters narrowly miss the lower confidence bound of 60 %;

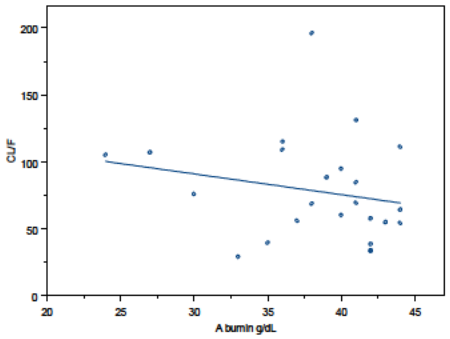
Additional analyses:



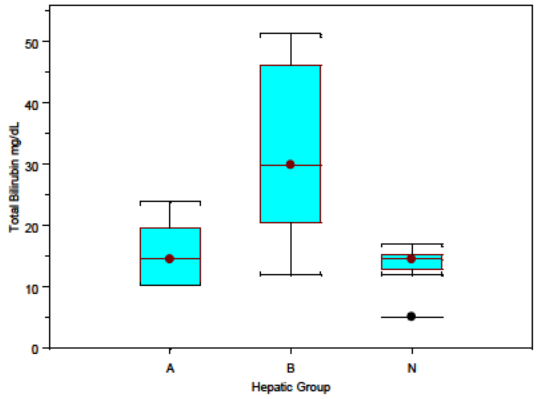


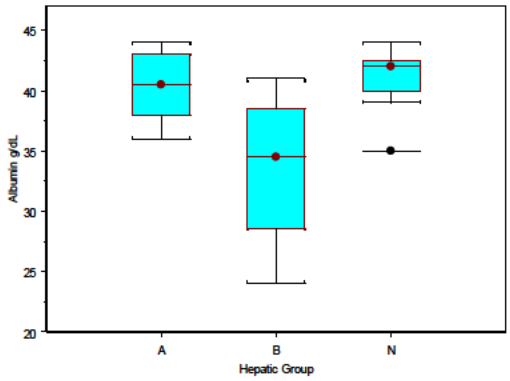




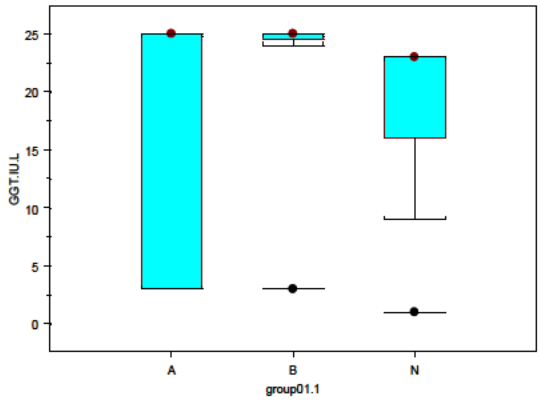


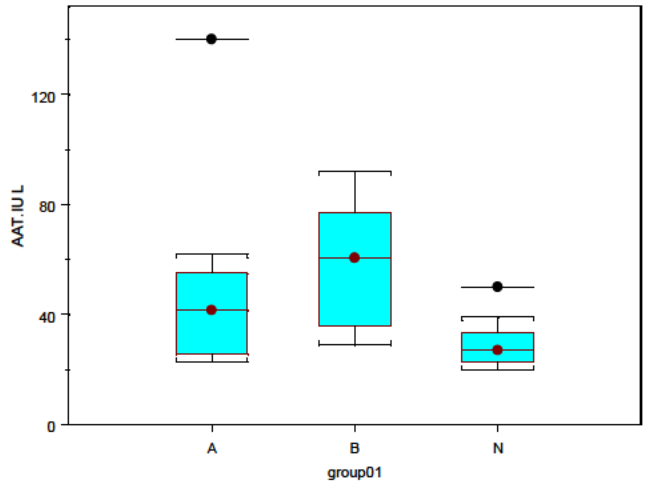
Above: Linear regression trends between liver parameters and exposure/PK parameters were not as one would anticipate when hepatic disease impairs drug clearance and exposures.

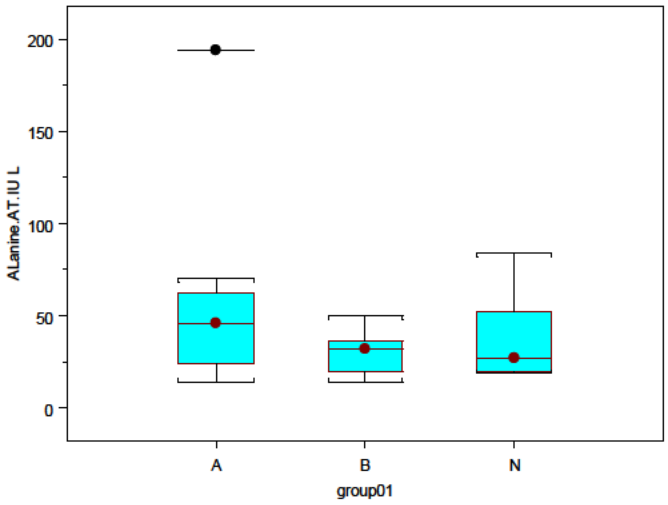


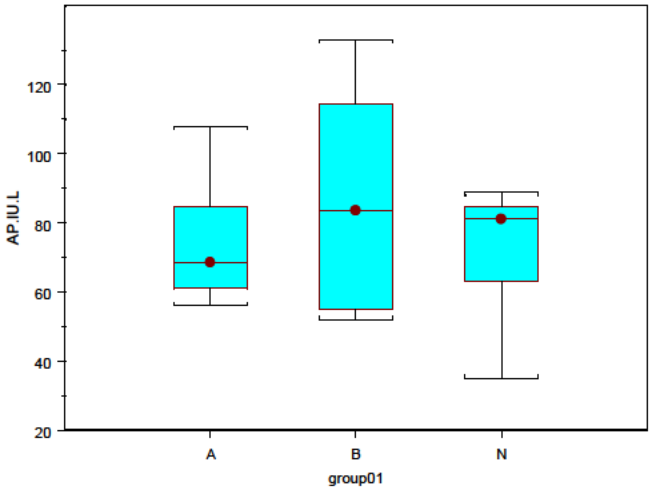


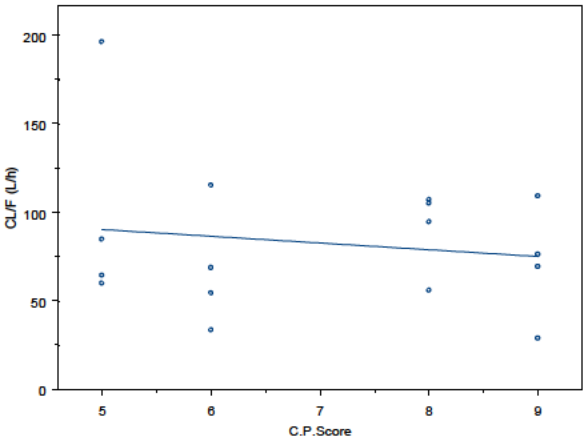
Above: Total bilirubin increased and albumin (synthetic function of liver) decreased in relation to worsening hepatic function (A = mild HI, B = Moderate HI, and N =Normal)

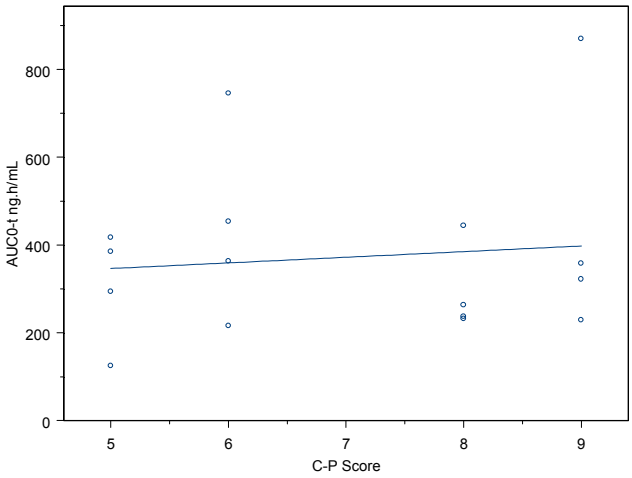


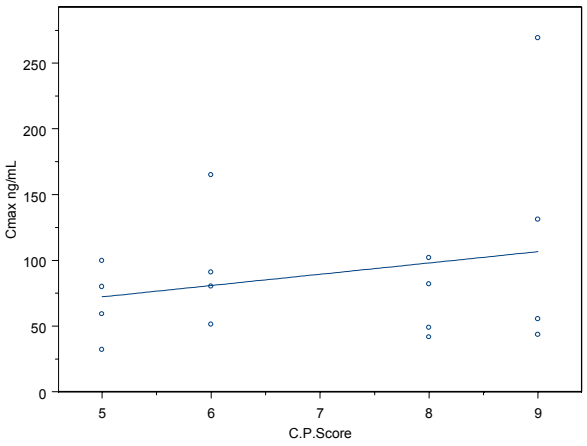



ALanine.AT.IU.L
200
150
100
50
0
A
B
N
group01

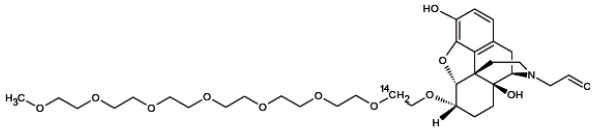

AP.IU.L
120
100
80
60
40
20
A
B
N
group01


CL/F (L/h)
200
150
100
50
0
5
6
7
8
9
C.P.Score





Mass Balance Study: A Phase I, Open-Label, Single-Centre Study to Assess Absorption, Distribution, Metabolism and Excretion (ADME) after [14C]-labeled Oral Administration of NKTR-118 to Healthy Male Volunteers

Compound code	[^{14}C]NKTR-118
Structural formula	

Primary objective

• To characterize the absorption, distribution, metabolism, and excretion (ADME) of a single oral dose of 25 mg [^{14}C]-labeled NKTR-118 in healthy male volunteers

Secondary objective

• To further describe the safety and tolerability of a single oral dose of 25 mg [^{14}C] NKTR-118 in healthy male volunteers

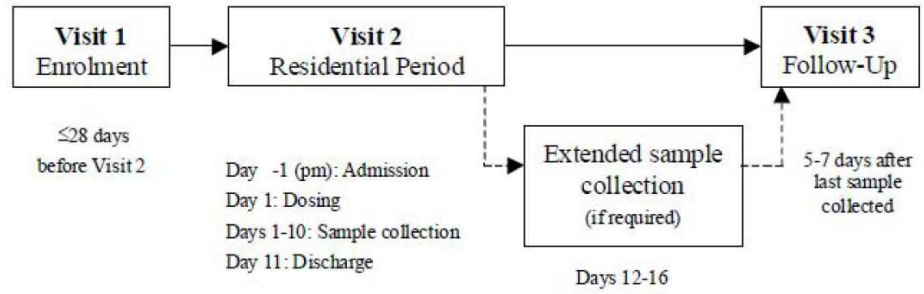
Exploratory objectives

• To identify and profile the metabolites in selected samples of urine, faeces, and plasma following a single oral dose of [^{14}C] NKTR-118

Design: This was a phase 1, open-label, single dose study in n= 6 healthy male volunteers (50 -65 years inclusive). Study included a screening period to determine eligibility (visit 1), a residential period [day -1 for baseline assessments, day 1 for dose administration, and up to day 11 (240 h after dosing) for blood, urine and feces sampling] or visit 2, and a follow up visit at 5- 7 days after the collection of last urine and/or feces samples (visit 3).

With respect to sample collection, if significant radioactivity was still being recovered after 240 h of sampling, additional 24 hour collections of urine and/or faeces was to continue on an out-patient basis up to a maximum of an additional 5 days. Sample collection was not to go beyond 16 days after the investigational product administration and could have been terminated earlier if >90% total recovery of radioactivity was achieved or radioactivity counts were <3 times the background count rate on 2 consecutive urine and faeces samples.

Figure 1 Flow chart of study design



Blood sampling: On day 1 at pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 16 h post dose; On days 2 to 11 at 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, and 240 h Post-dose.

Urine Collection: On day -1 pre-dose (-24 to 0 h), on day 1 at 0-6, 6-12, and 12-24 h post-dose, and on days 2 – 11, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, 192-216, and 216-240 h post-dose.

Fecal collection: On day -1 at pre-dose (-24 h to 0h), on day 1 from 0-24 h post-dose, on days 2- 11 at 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, 192-216, and 216-240 h post-dose intervals.

Vomitus was collected if it occurred after dosing on day 1 (0- 24 h post-dose).

Metabolite identification blood sampling was done on day 1 at pre-dose, 30 minutes, 2, 4, 6, 12 h post-dose and at 24 h post dose.

Dosing clarification: Dose was administered in the morning after overnight fasting and subjects were to fast for at least 4 h after dose. The dose containers were rinsed repeatedly with water as directed so that the total fluid volume including the dose did not exceed 240 mL. The volunteers were required to swallow the rinse and any remaining fluid.

Investigational product	Route of administration, dosage form, and strength	Manufacturer	Batch number
[^{14}C] NKTR-118	Oral solution, 27 mg containing 3.43 MBq in 10 mL 0.1 M citrate buffer	AstraZeneca	P8481

Based on the Analytical Summary Document for Drug Product of the [^{14}C] NKTR-118 solution, the nominal total dose was to be 25 mg (3.20 MBq ± 10% [78-95 µCi ± 10%]). The release data however showed 108% of label claim which was within the acceptance criterion. The content was verified by (b) (4) to be 27 mg (3.43 MBq) and the 6 volunteers were thus each administered 27 mg of investigational product. Hence in this Clinical Study Report, the actual dose administered is referred to as 27 mg and used for all analyses.

Variables for measurement:

PK: AUC, AUC(0-t), Cmax, tmax, t1/2, CL/F, and Vz/F for NKTR-118 and [14C] radioactivity in plasma and whole blood; Ae and fe of [14C] radioactivity in urine and faeces and of NKTR-118 in urine; plasma NKTR-118/plasma [14C] radioactivity ratios and whole blood [14C] radioactivity to plasma [14C] radioactivity ratios; distribution into red blood cells;

The statistical analyses of all safety data were performed by (b) (4) SAS® Version 9.2. Pharmacokinetic parameters were derived and summarized by (b) (4) WinNonlin Version 5.2 and SAS® Version 9.2.

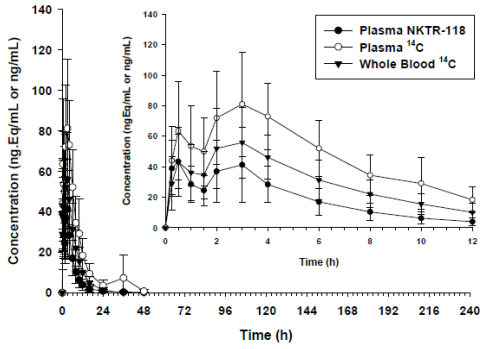
Safety: Adverse events, laboratory assessments, vital signs, physical examination, ECG

Results:

Plasma and whole blood concentrations/radioactivity and pharmacokinetics:

- Plasma NKTR-118 (cold; ng/mL) and plasma and whole blood radioactive concentrations (ngEq/mL) were detectable in all 6 subjects at the first post-dose sampling point (0.25 h).

- All subjects had detectable drug concentrations for up to 24 h post-dose in plasma, while 4/6 subjects had detectable NKTR-118 in plasma up to 48 h post-dose. Similarly plasma radioactivity (ngEq/mL) were noted in all subjects for up to 24 h post-dose, and up to 48 h post-dose in 4 to 5 subjects. Whole blood radioactivity was detectable in all subjects for up to 16 h post-dose; it remained detectable in 3/6 subjects at 24 h post-dose and in one subject at 36 h post-dose.
- Mean plasma radioactivity equivalent concentrations were greater than mean NKTR-118 plasma concentrations (cold) at all time points indicating that the radioactivity in plasma includes metabolite products in the systemic circulation. The ratio of plasma NKTR-118 (cold) to plasma radioactivity decreased over time [90% at 0.25 hours, 70% at 0.5 hours to approximately 9% to 31% by 16 hours postdose], indicating the formation and increase of metabolite levels over time.
- The range of whole blood to plasma radioactivity ratios indicates that 14C radioactivity does not distribute into erythrocytes to any meaningful extent. This is also demonstrated by the low total radioactivity (%) associated with red blood cells (range 0% at 24 hours to 13.8% at 3 hours).
- Two peak concentrations were noted within 4 h in most-individuals (see mean concentration-time profiles below) for both plasma concentrations and radioactivity indicating potential for enterohepatic recirculation. Mean concentrations peaked at a median time of 1.74 hours for plasma NKTR-118 and at 2.23 hours and 2.20 hours for radioactivity in plasma and whole blood, respectively.



Summary of key pharmacokinetic parameters and ratios are provided:

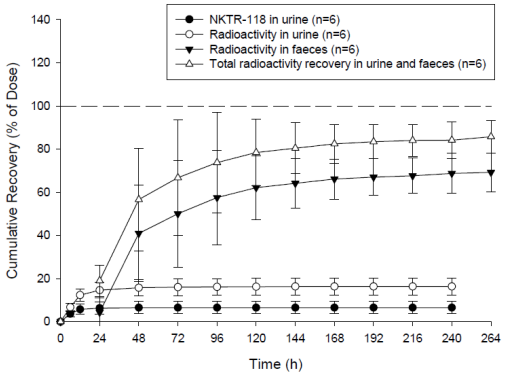
Parameter	n	Statistic	NKTR-118 plasma	Plasma radioactivity	Whole blood radioactivity
AUC[a] (ng*h/mL)	6	Geo. Mean (CV%)	233 (61.9)	710 (49.2)	392 (44.2)
C_{max}[a] (ng/mL)	6	Geo. Mean (CV%)	51.1 (38.3)	84.8 (40.3)	57.5 (40.8)
t_{max} (h)	6	Median (min, max)	1.74 (0.25, 3.02)	2.23 (0.50, 4.02)	2.20 (0.50, 4.02)
λ_z (1/h)	6	Geo. Mean (CV%)	0.0880 (46.5)	0.0952 (41.4)	0.190 (27.5)
$t_{½}$ (h)	6	Geo. Mean (CV%)	7.88 (46.4)	7.28 (41.4)	3.66 (27.5)
CL/F (L/h)	6	Geo. Mean (CV%)	116 (61.9)	38.0 (49.3)	69.0 (44.3)
Vz/F (L)	6	Geo. Mean (CV%)	1320 (54.6)	399 (25.2)	364 (22.6)
CL_R (L/h)	6	Geo. Mean (CV%)	6.92 (25.6)	5.83 (29.3)	-
C_{max}(PL)/ C_{max}(PR)	6	Geo. Mean (CV%)	0.602 (7.0)	-	-
AUC(PL)/ AUC(PR)	6	Geo. Mean (CV%)	0.327 (30.2)	-	-
C_{max}(WBR)/ C_{max}(PR)	6	Geo. Mean (CV%)	-	-	0.678 (3.9)
AUC(WBR)/ AUC(PR)	6	Geo. Mean (CV%)	-	-	0.551 (11.1)

CV% geometric coefficient of variation in percent; Geo. Mean geometric mean; PL NKTR-118 plasma; PR plasma radioactivity; WBR whole blood radioactivity

[a] For radioactivity AUC units are ngEq·h/mL and C_{max} units are ngEq/mL

Mass Balance (urine and feces recovery):

Cumulative amounts of radioactivity recovered in urine and fecal collections as well as their combined amounts in ngEq are shown in figure and table below:

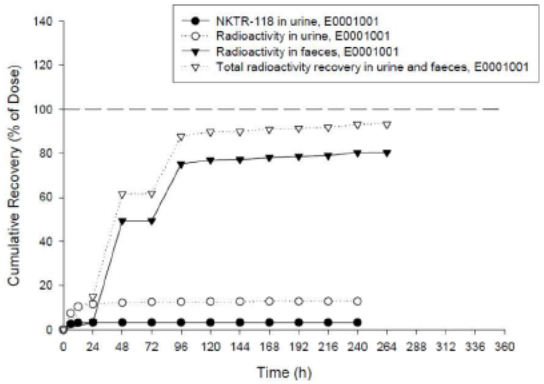


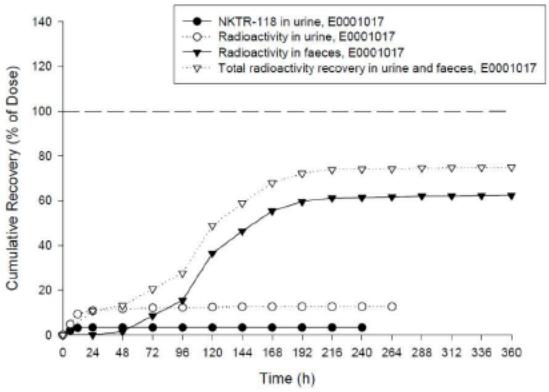
	NKTR-118 in Urine		Radioactivity in Urine		Radioactivity in Faeces[a]		Total Radioactivity	
	Dose recovered		Dose recovered		Dose recovered		Dose recovered	
Subject/ Statistic	ng	% dose	ngEq	% dose	ngEq	% dose	ngEq	% dose
E0001001	867000	3.21	3450000	12.8	21700000	80.4	25200000	93.2
E0001017	893000	3.31	3410000	12.6	16800000	62.3	20200000	74.9
E0001018	1860000	6.87	3950000	14.6	20900000	77.4	24900000	92.0
E0001031	2430000	9.01	5700000	21.1	17000000	62.9	22700000	84.1
E0001033	1700000	6.31	4220000	15.6	16700000	61.9	20900000	77.5
E0001037	2750000	10.2	5760000	21.3	17200000	63.8	23000000	85.2
n	6	6	6	6	6	6	6	6
Geometric mean	1590000	5.90	4310000	16.0	18300000	67.7	22700000	84.2
CV%	52.3	52.4	23.8	23.7	12.0	12.0	9.0	8.8
Minimum	867000	3.21	3410000	12.6	16700000	61.9	20200000	74.9
Maximum	2750000	10..2	5760000	21.3	21700000	80.4	25200000	93.2

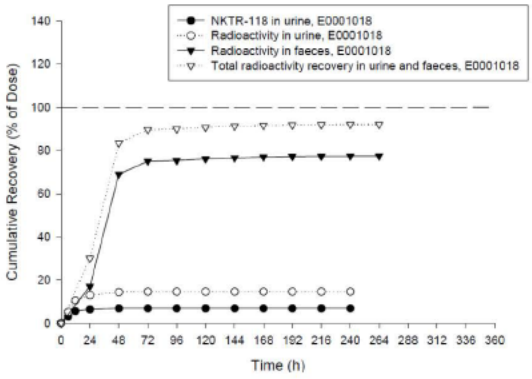
CV% geometric coefficient of variation in percent; n number of observations.
Note: The table summarises cumulative recoveries over a period of 240 hours postdose for urine and over a period of 360 hours postdose for faeces and total radioactivity.
[a] The collection interval for Volunteer E0001017 was extended to 360 hours. Preceding intervals were used for calculating cumulative excretion (see Section 7.6.1)

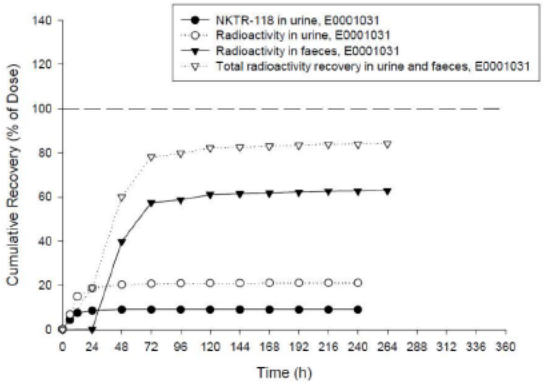
Together, urine and feces accounted for a mean total cumulative combined recovery of 84.2 % (74.2 % to 93.2 %) over the 240 h post-dose collections (4 subjects contributed samples up to 264 h). Most of the radioactivity was recovered in feces (67.7 %; range: 61.9 – 80.4 %) while ~ 16 % (range: 12.6 – 21.3 %) was recovered in urine. Thus the primary elimination pathway for total radioactivity per the findings of this study was via feces. Unchanged NKTR-118 recovered in urine was ~ 6 %, suggesting renal excretion may be a minor pathway for Naloxegol. Based on urinary recovery of dosed radioactivity, fraction absorbed of oral naloxegol dose appears to be at least 16 %. Based on the observed plasma concentrations to whole blood radioactivity ratios, majority of circulating radioactivity in plasma (~ 67 % of AUC) appears to be due to NKTR-118 metabolites. Lack of significant radioactivity in red blood cells indicates plasma to be an appropriate matrix for naloxegol and metabolite analyses. A 100 % dose recovery was not obtained in any individual in this study.

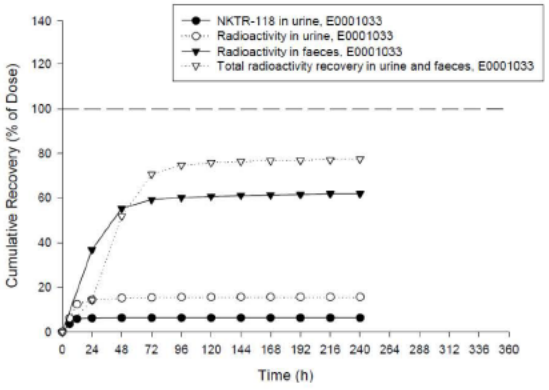
Individual mass balance (cumulative recovery) plots in study subjects:

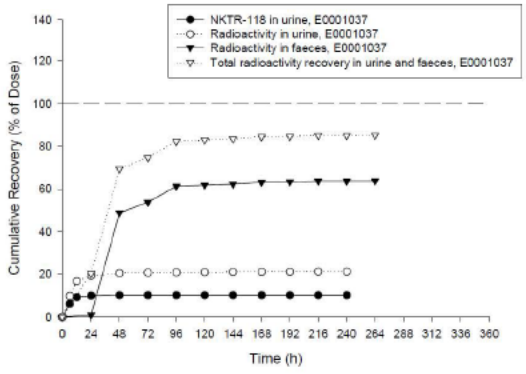

NKTR-118 in urine, E0001001
Radioactivity in urine, E0001001
Radioactivity in faeces, E0001001
Total radioactivity recovery in urine and faeces, E0001001
Cumulative Recovery (% of Dose)
Time (h)


NKTR-118 in urine, E0001017
Radioactivity in urine, E0001017
Radioactivity in faeces, E0001017
Total radioactivity recovery in urine and faeces, E0001017
Cumulative Recovery (% of Dose)
Time (h)


NKTR-118 in urine, E0001018
Radioactivity in urine, E0001018
Radioactivity in faeces, E0001018
Total radioactivity recovery in urine and faeces, E0001018
Cumulative Recovery (% of Dose)
Time (h)


NKTR-118 in urine, E0001031
Radioactivity in urine, E0001031
Radioactivity in faeces, E0001031
Total radioactivity recovery in urine and faeces, E0001031
Cumulative Recovery (% of Dose)
Time (h)


NKTR-118 in urine, E0001033
Radioactivity in urine, E0001033
Radioactivity in faeces, E0001033
Total radioactivity recovery in urine and faeces, E0001033
Cumulative Recovery (% of Dose)
Time (h)


NKTR-118 in urine, E0001037
Radioactivity in urine, E0001037
Radioactivity in faeces, E0001037
Total radioactivity recovery in urine and faeces, E0001037
Cumulative Recovery (% of Dose)
Time (h)

Safety:

APPEARS THIS WAY ON ORIGINAL

SYSTEM ORGAN CLASS/ Preferred term	Number (%) of subjects (N=6)
Subjects with any AE	2 (33.3%)
GASTROINTESTINAL DISORDERS	2 (33.3%)
Diarrhoea	2 (33.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (16.7%)
Fatigue	1 (16.7%)

Bioanalytical summary for mass balance study D3820C00001:

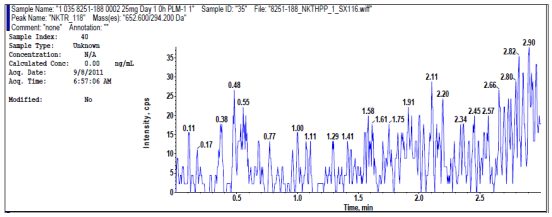
NKTR118 (Naloxegol) in plasma and urine were analyzed using validated analytical methods using solid phase extraction (plasma) or direct dilution (urine) followed by LC-MS/MS methodology ((b) (4) NKTHPP and NKTHUP). Internal standard used was AZ13337019, also known as [13C6]-NKTR_118. LLOQ in plasma and urine by these methods were 0.1 and 25 ng/mL respectively. Total number of plasma and urine samples assayed from the mass balance study were 144 and 78 respectively, stored at -10 to -30°C.

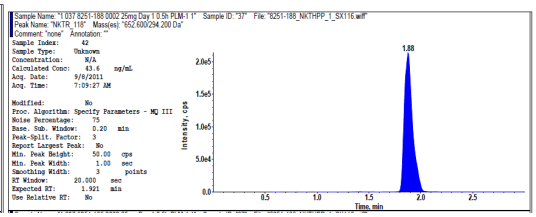
Analyses were performed in batches containing study samples, calibration standards at 8 concentration levels, QC samples at 3 undiluted concentration levels in duplicate, dilution QC samples (if the batch contained study samples requiring dilution), and blank samples. The criteria on calibration standards and undiluted QC samples for accepting an analytical batch was that at least three-fourths of back-calculated concentrations for calibration standards and at least two-thirds of the QC samples (at least one-half at each concentration level) should be within ±15.0% (±20.0% at LLOQ) from the nominal value. The criteria on dilution QC samples for accepting the diluted sample data was that at least one-half of the dilution QC samples (at each dilution) should be within ±15.0% from the nominal value.

The calibration and QC data for the assay met acceptance criteria. For the plasma analysis, the precision (%CV) and accuracy (% bias) for the QC samples at 3 concentrations were ≤3.0% and were within -2.7% to 0.4%, respectively, which indicated that the method performed reliably during the analysis of study samples. For the urine analysis, the accuracy (% bias) for the QC samples at 3 concentrations were within -1.0% to 1.5%, which indicated that the method performed reliably during the analysis of study samples. All study samples were reportedly analyzed within the established stability in human plasma and urine (185 days and 184 days, respectively).

ISR was not conducted for either plasma or urine samples in this study.

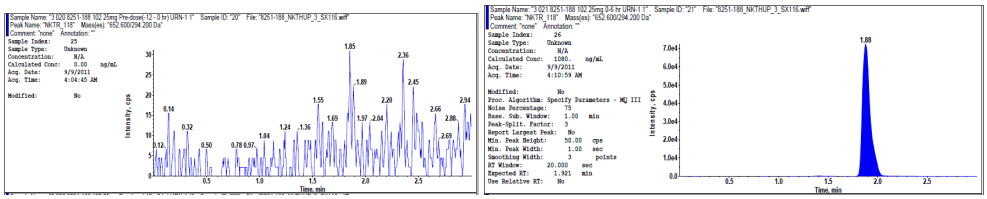
Plasma chromatograms from study subject 102 at pre-dose and 0.5 h post-dose:





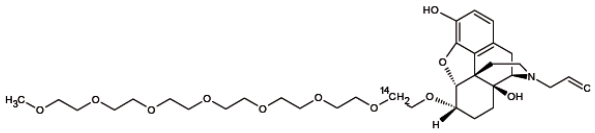
APPEARS THIS WAY ON ORIGINAL

Urine chromatograms from study subject 102 at pre-dose and 0-6 h post-dose:



APPEARS THIS WAY ON ORIGINAL

NKTR-118: Metabolism of NKTR-118 in Healthy Male Volunteers Following Oral Administration of [^{14}C] NKTR-118 (D3820C00001)

Compound code	[^{14}C]NKTR-118
Structural formula	

Objective and methodology: To investigate the metabolite profiles in plasma, urine and feces and characterize the structure of formed metabolites after oral administration of radio-labeled NKTR-118 in healthy male volunteers of the mass balance study D3820C00001. In this study, subjects were administered a single oral target dose of 25 mg (38.4 µmol, 3.20 MBq) [^{14}C]NKTR-118. Excreta for metabolite characterization were collected up to 240 h post dose and blood samples for metabolite characterization were collected at 0.5, 2, 4, 6, 12 and 24 h post dose. Plasma, urine and fecal samples were prepared for metabolite analysis. All samples were stored at –70oC. The plasma, urine and feces homogenates were shipped to AstraZeneca R&D Södertälje on dry ice. In the analyses, metabolites were separated by liquid chromatography, characterized by mass spectrometry and metabolite profiles were monitored using radiochemical detection.

Metabolite profiles were monitored in the 0.5, 2, 4 and 6 h plasma samples, pooled urine (0-24 h) and pooled faecal homogenates (0-120 h).

Scintillation analyses

The plasma, urine and feces (before and after sample preparation) were analysed with a Tri-carb 1900TR liquid scintillation analyser (Perkin Elmer, Boston, MA). The radioactivity from drug-material (measured for 3 min) was reported as disintegrations per minute (dpm), and was obtained after subtraction of background radioactivity (dpm from scintillation fluid). The feces homogenates was prepared for scintillation by oxidizer Model B07 (Packard, USA).

Results:

Metabolites in plasma: NKTR-118 and four metabolites were detected of which all (M13, M7, M10 and M1) were characterized in plasma. The major metabolite M10 accounted for up to 12% of the total radioactivity in the radiochromatograms.

Table 1 **Summary of metabolite profile data in plasma from healthy male volunteers after oral administration of 25 mg (38.4 µmol, 3.20 MBq) NKTR-118**

			Fraction of total peak area (%)[a]			
M#	R_t (rel. parent)[b]	R_t (min)	Plasma 0.5 hours[c]	Plasma 2 hours	Plasma 4 hours	Plasma 6 hours
NKTR-118	1.0	23.9	100	75	64	100
M13	0.79	19.0	nd[d]	4.7	10	nd
M7	0.82	19.6	nd	6.3	8.2	nd
M10	0.84	20.2	nd	9.5	12	nd
M1	0.90	21.5	nd	4.8	5.5	nd

[a] percentage of the total peak area in the radiochromatograms
[b] R_t metabolite/R_t NKTR-118
[c] collection time after dosing
[d] nd – not detected (below a S/N ratio of 3 in the radiochromatogram)

Metabolite profiling in urine: Within 24 h a mean of 15.4% of the administered radioactivity was recovered in urine from orally administered healthy male volunteers. In the radiochromatographic analyses of urine (pooled 0-24 h samples) five radioactive peaks, excluding the unchanged NKTR-118, were detected. NKTR-118 accounted for the major part of the radioactivity in urine 10% of the dose in healthy volunteers, whereas the major characterized metabolites (M13, M12, M7 and M10) together represented 4% of the dose. One uncharacterized urine metabolite (MX2) represented approximately 2%. The separately analyzed urine sample pool (0-6 h) contaminated with Triton X had a corresponding metabolite profile as the 0-24 h urine sample.

Table 2 **Summary of detected metabolites in urine expressed as average fractions of the oral administered dose of [^{14}C]NKTR-118 to healthy volunteers (25 mg, 38.4 µmol, 3.20 MBq)**

			[a] Fraction of dose (%)
M#	[b] Rt (rel. parent)	Rt min	Healthy male volunteers
			[c] 0-24h
NKTR-118	1.00	25.1	9.9
MX2[d]	0.68	17.2	1.8
M13	0.70	19.9	1.1
M12	0.80	20.2	0.4
M7	0.83	20.9	0.7
M10	0.85	21.4	1.5
Fraction of dose detected			15.4
Fraction of dose characterised			13.6

[a] The fraction of administered NKTR-118 in urine detected in the radiochromatogram
[b] R_t metabolite/R_t NKTR-118
[c] Collection time after administration
[d] MX denotes uncharacterized metabolite

Metabolite profiling in feces: Within 120 h a mean of 60% of the administered radioactivity was recovered in feces from orally administrated healthy male volunteers.

In the radiochromatographic analyses of pooled feces (0-120 h samples) six radioactive peaks, excluding unchanged NKTR-118, were detected. Five radioactive peaks were characterized which together represented 58% of the dose (Table 3). In feces major metabolites (M12, M10 and M1) represented together 34% of the dose. NKTR-118 accounted for up to 16% of the dose. The separately analyzed sample pool from M102 (120-196 h) showed similar metabolic profile as the pooled feces 0-120 h. A summary of metabolite profile data is shown in Table 3 and the metabolite profiles from the analysis in Figure 3.

Table 3 **Summary of detected metabolites in faeces expressed as average fractions of the oral administered dose of [^{14}C]NKTR-118 to healthy volunteers (25 mg, 38.4 µmol, 3.20 MBq)**

			[a] Fraction of dose (%)
M#	**[b] Rt (rel. parent)**	**Rt min**	**Healthy male volunteers**
			[c] 0-120h
NKTR-118	1.00	24.8	16.2
MX1[d]	0.49	12.1	2.2
M13	0.76	18.8	4.5
M12	0.81	20.2	9.1
M10	0.86	21.4	10.9
M1	0.90	22.3	13.7
M4	0.93	23.0	3.8
Fraction of dose detected			60.4
Fraction of dose characterised			58.2

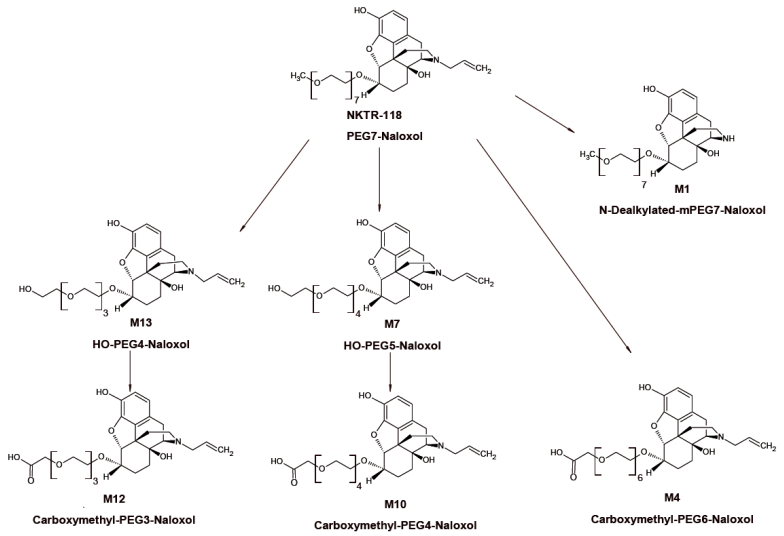
[a] The fraction of administered NKTR-118 in faeces detected in the radiochromatogram
[b] R_t metabolite/R_t NKTR-118
[c] Collection time after administration
[d] MX denotes uncharacterized metabolite

Characterization of metabolites: Structures of metabolites were determined using mass spectrometrical analyses of the radiochromatographically detected peaks.

The plasma metabolites were characterized as a partially shortened PEG chain products (M13 and M7) and M7 was further oxidized forming a carboxymethyl group at the end of the PEG chain (M10). Also an N-dealkylation product (M1) was detected in plasma. The urinary metabolites were also partially shortened PEG chain products (M13 and M7) and shortened PEG chain combined with oxidations forming carboxymethyls (M12 and M10). The carboxymethyl group was confirmed by an H/D exchange MS experiment. The major faecal metabolites were an N-dealkylation product (M1) and two carboxymethyl metabolites with different losses of the PEG chain (M12 and M10).

Sponsor claims that no radiochromatographic peak corresponds to naloxone or naloxol.

The sponsor's proposed metabolic pathway of NKTR-118 in man is shown:



M#	LC-RAM Rt (min)	*m/z* [a]	Δ*m/z* [b]	Proposed transformations	Comment[c]
NKTR-118	25.1	652	-	Unchanged molecule	P, F, U
MX1	12.1	nc	na	na	F
MX2	17.2	418	234	Partial loss of PEG	U
M13	19.9	506	146	Partial loss of PEG	P, F, U
M12	20.2	520	132	Partial loss of PEG and oxidation	F, U
M7	20.9	550	102	Partial loss of PEG	P, U
M10	21.4	564	88	Partial loss of PEG and oxidation	P, F, U
M1	21.5	612	40	Dealkylation	P, F
M4	23.0	652	0	Partial loss of PEG and oxidation	F

[a] Observed *m/z* for unlabelled pseudomolecular ion
[b] Difference vs. *m/z* of NKTR-118
[c] Metabolite detected in radiochromatogram of P=plasma, U=urine and/or F= faeces

Conclusions:

The elimination of NKTR-118 was moderate and the major fraction of radioactivity was excreted within 96 h. The radioactivity was excreted mainly via feces and approximately one fourth of the characterized drug-material in feces was excreted as parent compound. The major circulating species were unchanged NKTR-118, two partially shortened PEG chain products (M13 and M7) and an oxidized shortened PEG chain product (M10) and an N-dealkylation product (M1). The major metabolic pathways of NKTR-118 were cleavages of PEG chain followed by oxidation of the PEG moiety and accounted for 32% of the administered dose. Approximately 92% of the radiochromatographic peaks in the 0-24 h urine and 0-120 h feces samples were characterized.

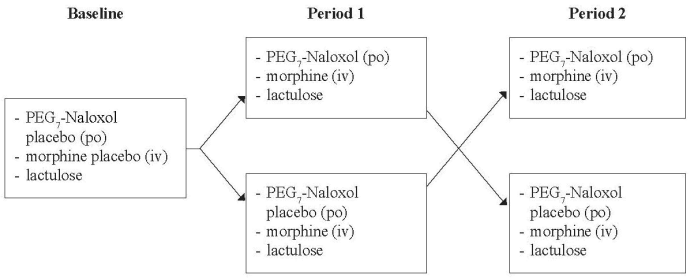
Comments: Overall, it appears that ~ 10 % and 16 % of the administered dose of naloxegol showed up as unchanged drug in urine and feces based on radiochromatographic analyses used in this metabolite profiling study of samples from the mass balance study. ~ 44 % of dose appeared in feces as metabolites; it may be likely that the absorption of naloxegol or NKTR-118 following oral administration may be more than what has been assumed based on unchanged drug in urine alone. However, it cannot be ruled out that metabolites noted in feces were formed from local degradation within the GI tract without systemic absorption of naloxegol.

05-IN-OX001: **A double-blind, placebo-controlled, dose escalation crossover study to evaluate antagonism of single oral doses of PEG7-Naloxol on peripheral and central effects of morphine in healthy male subjects**

Sponsor: Nektar Therapeutics; CRO: (b) (4); Bioanalytical Lab: (b) (4)

Objectives: The primary objectives of this study were to evaluate: □ the safety and tolerability of PEG7-Naloxol; □ the potential antagonistic effect of PEG7-Naloxol on morphine-induced delay in orocecal transit time; □ the potential antagonistic effect of PEG7-Naloxol on morphine-induced pupil constriction (miosis). The secondary objective of this study was to evaluate: □ the pharmacokinetics of PEG7-Naloxol and its glucuronide metabolite.

Design and samples size: This was a double-blind, placebo-controlled, dose escalation, crossover study of PEG7-Naloxol. Study included 3 periods; First was a baseline period which determined study eligibility by means of hydrogen breath test for estimation of orocecal transit time following administration of lactulose; second & third periods were treatment periods wherein subjects received in a crossover manner morphine i.v. dose (1-minute i.v. infusion of 5 mg/70 kg morphine) with PEG7-Naloxol oral dose (8, 15, 30, 60, 125, 250, 500, or 1000 mg; oral solution) in period 1, and morphine i.v. with PEG7-Naloxol placebo in period 2 or vice versa. Lactulose was given in both the periods to evaluate orocecal transit time by means of the hydrogen breath test. The orocecal transit time was defined as the time between lactulose ingestion and the earliest detectable rise in hydrogen >5 ppm above baseline for 3 consecutive samples; Escalation to sequential dose levels was staggered by 7 days. Dose escalations were based on safety and tolerability of the preceding dose level.



APPEARS THIS WAY ON ORIGINAL

Forty-eight (48) healthy male subjects 18 -45 years of age were enrolled in the Treatment Periods and analyzed, 6 subjects per dose level. All eight (8) planned dose levels were evaluated.

PK and PD assessments: Peripheral antagonistic effect of PEG7-Naloxol was evaluated by mean % change in orocecal transit time. Central antagonistic effect of PEG7-Naloxol was evaluated by % change in mean pupil diameter over time (AUC). PK of PEG7-Naloxol and glucuronide metabolite were assessed as well.

$$\text{Percent Change in OCTT} = \left(1 - \frac{\left(OCTT_{Morphine+PEG_7Naloxol} - OCTT_{Baseline}\right)}{\left(OCTT_{Morphine+Placebo} - OCTT_{Baseline}\right)}\right) \text{ X } 100$$

APPEARS THIS WAY ON ORIGINAL

Results:

Effect of PEG7-Naloxol on morphine induced delay of OCTT- Peripheral effect:

Median data for percentage change in OCTT suggests antagonizing effect of PEG7-Naloxol on morphine induced delay in OCTT but the relationship to dose is not very consistent. There is also missing information due to uninterpretable results from 8 subjects. Sponsor's PD modeling suggested plateauing of effect at doses above 125 mg.

Table 1 Percent Change in OCTT in Subjects Receiving 8 mg to 1000 mg PEG_7-Naloxol

PEG_7-Naloxol Dose (mg)	N	Percent Change in OCTT		
		Median	Minimum	Maximum
8	6	0	-20	31
15	4	28	-9	147
30	6	100	22	200
60	5	26	-60	166
125	3	76	-50	100
250	4	34	26	100
500	5	50	-253	73
1000	6	83	-134	102

Individual data on OCTT for all doses of PEG7-Naloxol:

Out of total 48 subjects dosed, 38 subjects had data for all three treatment periods (baseline; morphine i.v. alone; and morphine with PEG7-Naloxol);

4/38 subjects with both baseline and post-baseline data showed a decrease in OCTT, contrary to the anticipated increase in orocecal transit time with morphine. In these 4 subjects, further dosing with PEG7-Naloxol either increased the OCTT relative to baseline or resulted in OCTT values similar to baseline.

Across dose levels, 34 subjects with both baseline and post-morphine data showed a clear increase in OCTT from baseline following administration of i.v. morphine.

25/ 40 subjects with both post-morphine and post-PEG7-Naloxol data showed a reduction in morphine-induced OCTT following administration of PEG7-Naloxol. In the remaining 15 subjects, 5 subjects had OCTT values following morphine that were unchanged with or without PEG7-Naloxol, while 10 subjects actually had higher OCTT values after PEG-7 Naloxol compared to those values on morphine alone.

7/25 subjects who were responded positively to PEG7-Naloxol treatment (i.e. a decrease in morphine induced prolongation of OCTT), had OCTT values that were at or below their baseline (pre-morphine) values.

PD responders were as follows by dose group: 2 (8 mg), 2 (15 mg), 4 (30 mg), 3 (60 mg), 2 (125 mg), 4 (250 mg), 2 (500 mg), and 5 (1000 mg).

A reduction to pre-morphine OCTT baseline values were noted as follows by dose group: 1 (60 mg), 1 (125 mg), 1 (250 mg), and 3 (1000 mg).

Dose (mg)	Subject Number	Baseline OCTT (min)	Morphine + Placebo OCTT (min)	Morphine + PEG_7-Naloxol OCTT (min)
8	101	50	125	140
8	102	20	80	80
8	103	66	170	140
8	105	20	125	125
8	106	66	260	200
8	107	80	110	110
15	202	68	66	170
15	203	96	66	110
15	205	80	231	245
15	208	20	ND	140
15	209	35	95	66
15	210	ND[3]	102	95
30	302	20	21	20
30	303	32	290	234
30	304	80	50	80
30	306	170	250	140
30	307	140	155	125
30	308	36	203	125
60	401	110	ND	125
60	402	110	231	200
60	403	110	246	20
60	404	35	82	110
60	405	ND[3]	110	35
60	406	20	51	51
125	501	35	ND	80
125	502	112	ND	ND
125	503	20	51	20
125	504	80	215	113
125	505	65	125	155
125	506	140	ND	ND
250	601	50	170	125
250	602	5	ND	38
250	604	20	50	20
250	605	39	140	110
250	606	20	ND	ND
250	607	50	111	95
500	701	80	125	200
500	702	20	ND	170
500	704	66	185	110
500	707	20	80	36
500	709	80	97	140
500	710	110	231	170
1000	802	96	140	95
1000	803	66	113	80
1000	804	80	110	81
1000	806	80	133	110
1000	807	20	65	20
1000	808	36	80	139

Effect of PEG7-Naloxol on morphine induced pupillary constriction (miosis)- Central effect:

A lack of central antagonism by PEG7-Naloxol on morphine-induced pupillary constriction (miosis) was more readily apparent, especially at doses up to 125 mg compared to its antagonism of peripheral (OCTT delay) effects:

PEG_7-Naloxol Dose (mg)	Number of Subjects with Possible Change* in Pupil Diameter Versus Time Profiles Relative to Placebo
8	0/6
15	0/6
30	0/6
60	0/5**
125	0/6
250	1/6
500	0/5**
1000	1/6

* Possible Change = subject's PD difference-time profile exceeded their respective 95% CI limits on 2 or more sequential occasions.

** Subjects 401 (60 mg) and 702 (500 mg) did not receive both treatments

Partial reversal of morphine-induced miosis after PEG7-Naloxol may have occurred in one subject at the 250 mg and one at the 1000 mg dose levels.

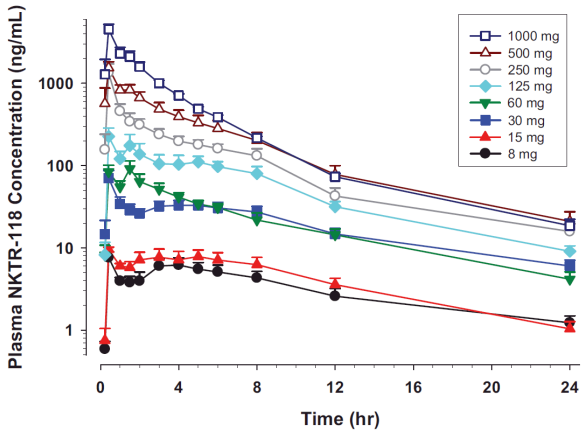
Conclusions: The PD measurement used in this study for evaluating peripheral antagonism by PEG7-Naloxol (OCTT measurement by H2 breath test following lactulose) does not appear to be very robust. Results were uninterpretable for several individuals across doses; sponsor also reports to have used 'extrapolation' for determining the OCTT values in each period as opposed to their pre-specified definition for OCTT based on 3 consecutive increases in hydrogen of > 5 ppm; the study failed to consistently demonstrate increase in OCTT with morphine; however, the majority of individuals dosed with morphine did show a prolongation of their OCTT from baseline, which then was reversed partially or in some cases completely by PEG7-Naloxol treatment in several individuals.

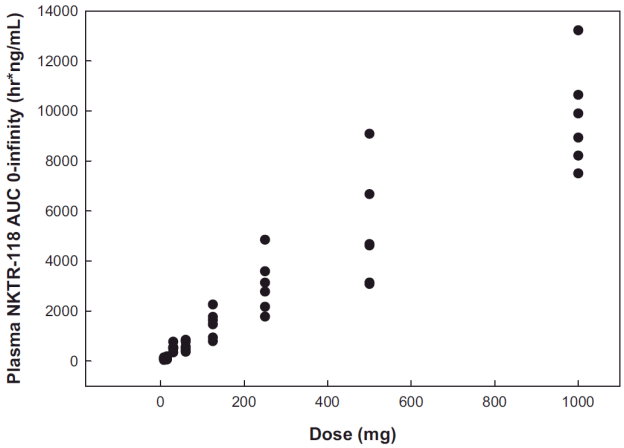
While results of this exploratory study are suggestive of peripheral antagonism of opioid induced GI effects by PEG7-Naloxol, neither a consistent trend in dose-response nor a definitive dose could be recognized from this study alone. Study did demonstrate that the central effects of opioids (based on pupillary constriction i.e. miosis) were not antagonized by PEG7-Naloxol treatment, at least at doses up to 125 mg.

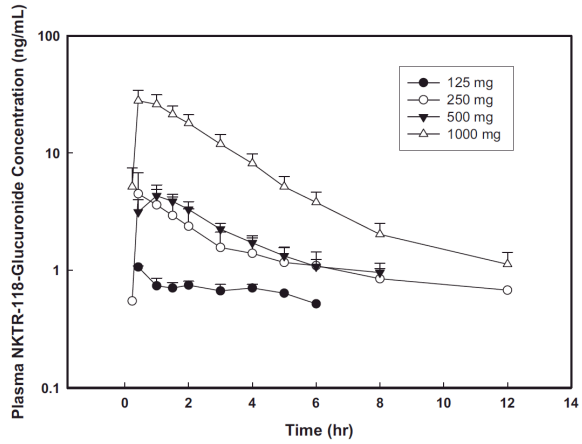
PK of naloxegol (solution):

Dose Group	Dose (mg)	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (hr·ng/mL)	$AUC_{0\text{-}\infty}$ (hr·ng/mL)	Extrapolated AUC (%)	Half-Life (hr)
1	8	1.88 (93.7)	9.46 (24.9)	77.1 (41.3)	96.8 (39.3)	18.8 (76.6)	9.928 (55.4)
2	15	1.44 (112.4)	10.94 (26.9)	102.5 (47.4)	112.0 (47.9)	8.4 (20.8)	6.349 (9.8)
3	30	1.01 (144.2)	72.72 (51.6)	462.2 (25.5)	536.5 (25.6)	13.5 (55.4)	8.001 (29.1)
4	60	0.88 (61.0)	112.88 (36.4)	547.4 (30.1)	587.0 (32.4)	6.2 (38.2)	6.227 (16.9)
5	125	1.38 (101.2)	327.33 (39.5)	1404.7 (37.4)	1476.4 (36.8)	4.9 (33.9)	5.430 (16.7)
6	250	0.42 (44.1)	1337.33 (88.5)	2925.78 (58.6)	3047.4 (35.9)	4.0 (67.8)	4.978 (18.1)
7	500	0.48 (54.7)	1608.50 (40.7)	5068.1 (43.5)	5213.0 (44.2)	2.5 (54.1)	4.560 (11.1)
8	1000	0.60 (74.0)	4716.67 (27.3)	9623.7 (20.9)	9734.3 (21.0)	1.1 (57.9)	3.875 (17.0)

N=6 healthy subjects per dose level.





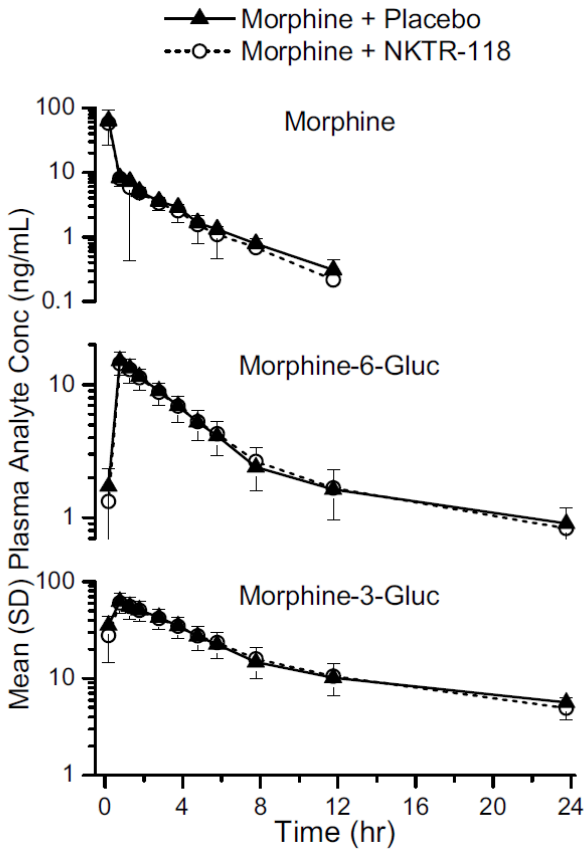


PK of morphine: In this study the plasma samples for investigation of NKTR-118 pharmacokinetics were assayed for morphine, morphine-3-glucuronide, and morphine-6-glucuronide to allow comparison of the pharmacokinetics of morphine and its metabolites after administration of morphine with NKTR-118 and morphine with placebo, to investigate possible drug-drug interactions between NKTR-118 and morphine.

Within subjects, plasma concentration-time profiles for all analytes were comparable, independent of treatment i.e. naloxegol dose. Individual subject profiles were also comparable within and across naloxegol dose cohorts,

indicating that concurrent administration of NKTR-118 had no effect on the pharmacokinetics of IV Morphine. Thus sponsor utilized pooled concentration-time data for PK and statistical analyses to evaluate DDI potential for assessing effect of naloxegol on morphine:

Mean plasma concentration-time profiles for morphine and metabolites pooled across dose cohorts were essentially superimposable, independent of treatment, as shown in the following figure.



Morphine PK parameters:

Parameter	Units	N	Morphine+NKTR-118	Morphine+Placebo
C_{max}	ng/mL	42	57.95 (33.08)	63.58 (36.89)
$AUC_{(0\text{-last})}$	hr.ng/mL	42	44.72 (15.49)	50.09 (18.33)
$AUC_{(0\text{-inf})}$	hr.ng/mL	42	46.50 (15.76)	51.80 (18.49)

Morphine-3-glucuronide PK parameters:

Parameter	Units	N	Morphine+NKTR-118	Morphine+Placebo
C_{max}	ng/mL	46	61.98 (14.85)	63.35 (15.63)
$AUC_{(0\text{-last})}$	hr.ng/mL	46	411.48 (95.85)	414.11 (102.45)
$AUC_{(0\text{-inf})}$	hr.ng/mL	46	472.70 (109.19)	498.17 (122.99)

Morphine 6-glucuronide PK parameters:

Parameter	Units	N	Morphine+NKTR-118	Morphine+Placebo
C_{max}	ng/mL	46	14.76 (2.82)	15.40 (3.40)
$AUC_{(0\text{-last})}$	hr.ng/mL	46	77.21 (15.59)	77.54 (19.04)
$AUC_{(0\text{-inf})}$	hr.ng/mL	46	88.22 (19.08)	91.21 (22.29)

Ratios of Morphine+NKTR-118 to Morphine+Placebo Least-Square Mean Cmax and AUC values for morphine and both metabolites are shown. The 90% CIs for Morphine+NKTR-118 to Morphine+Placebo ratios for Cmax, AUC(0-last), and AUC(0-inf) values for all analytes were within the 80% to 125% interval used to determine bioequivalence, except the lower 90% CI limit for morphine Cmax was 78.4%.

	Ratio of Morphine+NKTR-118/ Morphine+Placebo Least-Square Means (% of Morphine+Placebo Least-Square Mean)		
Analyte	**C_{max}**	**$AUC_{(0\text{-last})}$**	**$AUC_{(0\text{-inf})}$**
Morphine	92.8	90.8	91.2
Morphine-3-glucuronide	98.9	100.5	95.4
Morphine-6-glucuronide	97.1	101.5	97.3

Statistical Analysis of Log-Transformed Pharmacokinetic Parameters for Morphine

Log Transformed	Contrast	Ratio (%)	pvalue	Power	90% Confidence Interval	
					Lower	Upper
C_{max}	Morphine+NKTR-118/ Morphine+Placebo	92.8	0.464	0.699	78.3	110.0
$AUC_{(0\text{-last})}$	Morphine+NKTR-118/ Morphine+Placebo	90.8	0.099	0.984	82.5	100.0
$AUC_{(0\text{-inf})}$	Morphine+NKTR-118/ Morphine+Placebo	91.2	0.105	0.988	83.1	100.1

Statistical Analysis of Log-Transformed Pharmacokinetic Parameters for Morphine-3-Glucuronide

Log Transformed	Contrast	Ratio (%)	P value	Power	90% Confidence Interval	
					Lower	Upper
C_{max}	Morphine+NKTR-118/ Morphine+Placebo	98.9	0.767	0.9999	92.8	105.4
$AUC_{(0\text{-last})}$	Morphine+NKTR-118/ Morphine+Placebo	100.5	0.891	0.9999	94.3	107.1
$AUC_{(0\text{-inf})}$	Morphine+NKTR-118/ Morphine+Placebo	96.1	0.318	0.9999	90.1	102.7

Statistical Analysis of Log-Transformed Pharmacokinetic Parameters for Morphine-6-Glucuronide

Log Transformed	Contrast	Ratio (%)	P value	Power	90% Confidence Interval	
					Lower	Upper
C_{max}	Morphine+NKTR-118/ Morphine+Placebo	97.1	0.401	1.000	91.7	102.9
$AUC_{(0\text{-last})}$	Morphine+NKTR-118/ Morphine+Placebo	101.5	0.740	0.999	94.3	109.3
$AUC_{(0\text{-inf})}$	Morphine+NKTR-118/ Morphine+Placebo	98.4	0.709	0.999	91.5	105.8

Concomitant administration of morphine with NKTR-118 did not affect the pharmacokinetics of morphine, morphine-3-glucuronide, and morphine-6-glucuronide.

D3820C00020- A Phase I, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability and Pharmacokinetics of NKTR-118 following single and multiple ascending oral dose administration in healthy young and elderly Japanese subjects, and An Open, Randomized, Crossover Study to Investigate the Effect of Food on the Pharmacokinetics after single oral doses of NKTR-118 in healthy male young Japanese subjects

Design:

This study consisted of two study parts, i.e., a single and multiple ascending dose part (S+MAD part: Panels 1-5) and cross-over study part to investigate the effect of food (Effect of food part: Panel 6).

S+MAD part was a, Randomized, Double-Blind, Placebo-Controlled Study to assess the safety, tolerability and pharmacokinetics of NKTR-118 following single and multiple oral dose administration in healthy young subjects aged 20 to 45 years and elderly Japanese subjects aged 65 to 80 years.

Each panel consisted of 8 healthy Japanese subjects with 6 subjects receiving active drug and 2 receiving placebo. Subjects received a single dose at Day 1, followed by 8-day once daily multiple doses (during Days 3 - 10). Young subjects received 12.5, 25, 50 and 100 mg of NKTR-118/placebo as a single dose and once daily multiple doses. Elderly subjects received 25 mg of NKTR-118/placebo as a single dose and once daily multiple doses.

Effect of food part was an Open, Randomized, Two-treatment (dosing condition), 2-period, 2- sequence crossover study with single oral administration to healthy male young Japanese subjects aged 20 to 45 years. A total of 10 subjects were randomized in this part.

Two single dose administrations (one in each of the two consecutive treatment periods) were separated by a washout period of at least 7 days between the two dosing. "Fasting" was defined as deprivation of food for ≥10 hours, whereas "fed" was defined as administration of the drug 30 minutes after the subjects complete a standardized low fat breakfast (700 kcal or less with 20% or less of fat) within 20 minutes.

The following study objectives and variables were evaluated:

Objective			Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To assess the safety and tolerability of NKTR-118 following single and multiple ascending oral doses of NKTR-118 in healthy young and elderly Japanese subjects under fasting and fed conditions.	Adverse events Laboratory variables Physical examination ECG Vital signs
Secondary	PK	To characterise the PK of NKTR-118 following single and multiple dosing of NKTR-118 in healthy young and elderly Japanese subjects under fasting conditions.	After single dose: AUC, $AUC_{(0-t)}$, CL/F, C_{max}, t_{max}, $t_{1/2\lambda z}$, V_z/F, CL_R, A_e, f_e% After multiple doses: AUC_{ss}, $AUC_{(0-t),ss}$, $AUC_{\tau,ss}$, CL/F_{ss}, $C_{max,ss}$, C_{trough}, $t_{max,ss}$, $t_{1/2\lambda z,ss}$, V_z/F_{ss}, $R_{ac(AUC)}$, $R_{ac(Cmax)}$, time dependency of the pharmacokinetics evaluated by $AUC_{\tau,ss}$/AUC (single dose), $CL_{R,ss}$, $A_{e,ss}$, $f_{e,ss}$%
		To evaluate the effects of food, in comparison to fasting condition, on pharmacokinetics of NKTR-118 following single oral administration of NKTR-118 in healthy male Japanese subjects.	

APPEARS THIS WAY ON ORIGINAL

Statistical analyses:

To investigate dose proportionality of AUCss, a power model was assumed.

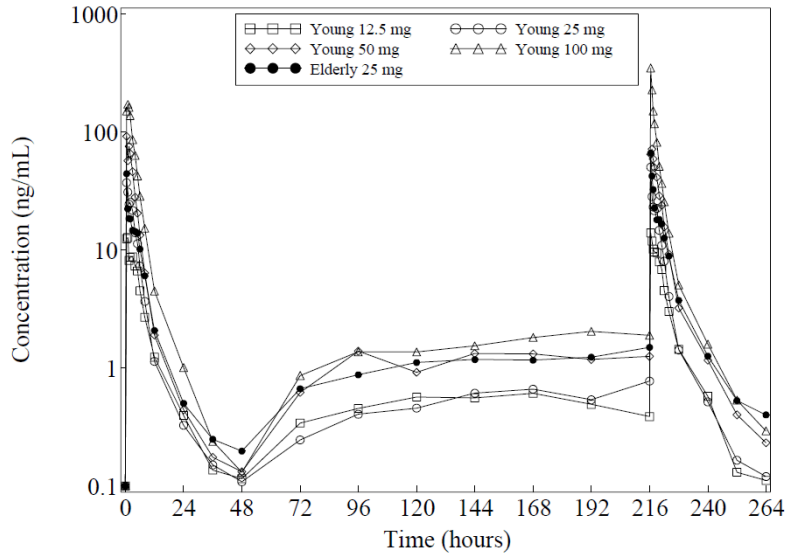
$AUCss = \alpha \bullet dose^{\beta} \bullet \varepsilon$, where α and β were parameters and ε a random error. In practice, this model was to be fitted to data using a linear regression model with the logarithm of AUCss as a response variable and the logarithm of dose as an explanatory variable. Dose proportionality was assessed by estimating β and its 2-sided 95% confidence interval. If the confidence interval had not crossed 1, then dose proportionality was to be ruled out.

In order to investigate the food-effect, the primary pharmacokinetic variables AUC and Cmax were log-transformed before analysis. They were analysed using a mixed-effect ANOVA model with fixed effects for sequence, period and dosing condition and a random effect for subject nested within sequence. Estimates and 90% confidence intervals of the means of the dosing conditions and the difference between dosing conditions were constructed in the logarithmic scale. By taking anti-logarithms, estimates and confidence intervals for the true geometric means and ratios of true geometric means were achieved. All confidence intervals were two-sided. Estimates and 90% confidence intervals of the true ratio of geometric means were presented for AUC (fed) / AUC (fasting) and Cmax(fed) / Cmax(fasting). Similarly, the analysis was done for AUCτ.

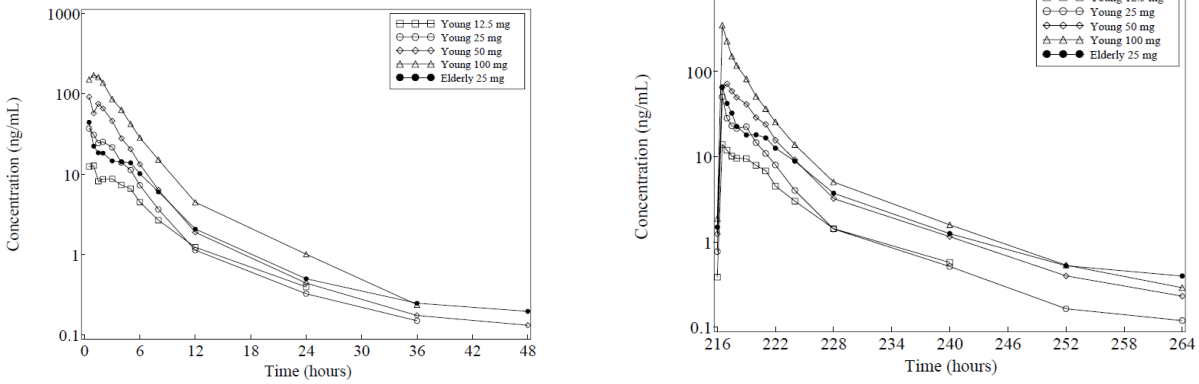
Results: Plasma concentrations were comparable between day 1 and day 10 in young healthy volunteers; Individual profiles exhibited multiple peaks as previously observed; Steady-state appears to have been achieved within 5 to 6 days of daily dosing based on visual inspection.

Plasma naloxegol concentration vs. time curves in healthy young and elderly Japanese volunteers following single and multiple doses are shown:

Geometric mean plasma concentrations (ng/mL) of NKTR-118 versus planned time following single and multiple dose administration of NKTR-118 in young and elderly healthy volunteers, Log-linear plot, Days 1 to 10 (PK analysis set)



Geometric mean plasma concentrations (ng/mL) of NKTR-118 versus planned time following single and multiple dose administration of NKTR-118 in young and elderly healthy volunteers. Log-linear plot, 0-48 h, Day 1 (upper) and Day 10 (lower) (PK analysis set)



Excretion in urine: Overall, the majority of the amount of NKTR-118 excreted in urine during a time period of 48 hours post-dose was collected within 24 hours after dosing of 25 mg NKTR-118. The geometric mean fraction of NKTR-118 excreted unchanged in urine within 24 hours (fe [0-24]) or 48 hours (fe [0-48]) after single dosing was 4.49% or 4.54% in young healthy volunteers, and 4.13% or 4.22% in elderly healthy volunteers. The corresponding values after multiple dosing were 4.77% or 4.83% in young healthy volunteers, and 5.60% or 5.95% in elderly healthy volunteers.

Single dose PK:

Summary of pharmacokinetic parameters of NKTR-118 for single dosing in SAD+MAD part

Variable (SI-unit)	Age group	Treatment	n	Geometric mean	CV(%)	Arithmetic mean	SD	Median	Min	Max
AUC(0-24) (hr*ng/mL)	Young	12.5 mg	6	76.34	31.32	79.82	29.71	71.45	59.8	139.5
		25 mg	6	148.17	28.02	152.93	42.29	143.70	113.2	207.7
		50 mg	6	326.42	59.97	364.52	161.17	419.65	137.6	528.5
		100 mg	6	721.34	67.12	836.87	480.08	741.75	342.1	1525.7
	Elderly	25 mg	6	165.20	63.47	192.42	127.83	162.50	86.3	435.4
AUC(0-t) (hr*ng/mL)	Young	12.5 mg	6	78.99	29.92	82.23	28.72	72.35	59.8	139.5
		25 mg	6	150.93	27.49	155.60	42.08	146.55	116.7	207.7
		50 mg	6	330.00	60.97	369.55	164.89	426.65	137.6	534.0
		100 mg	6	728.65	67.11	844.95	482.61	752.10	342.1	1531.1
	Elderly	25 mg	6	171.91	67.01	202.70	138.23	167.50	86.3	462.6
AUC (hr*ng/mL)	Young	12.5 mg	6	81.92	32.43	85.90	32.89	74.40	60.7	151.7
		25 mg	6	152.95	26.95	157.50	41.84	147.80	118.5	209.5
		50 mg	6	331.51	60.93	371.22	165.61	428.05	138.3	535.6
		100 mg	6	730.76	66.95	846.87	482.58	754.85	343.3	1532.7
	Elderly	25 mg	6	174.14	67.39	205.47	139.58	169.10	87.0	466.2
Cmax (ng/mL)	Young	12.5 mg	6	18.28	32.12	18.97	5.11	19.40	10.2	25.7
		25 mg	6	42.48	41.93	45.53	19.51	41.80	24.2	81.2
		50 mg	6	127.36	76.71	152.12	93.47	156.50	53.5	307.0
		100 mg	6	254.13	112.81	375.38	417.66	211.50	93.3	1200.0
	Elderly	25 mg	6	48.77	50.04	54.40	32.55	42.80	32.0	119.0
tmax (hr)	Young	12.5 mg	6					1.500	0.50	3.00
		25 mg	6					0.500	0.50	1.00
		50 mg	6					1.500	0.50	2.00
		100 mg	6					0.500	0.50	1.50
	Elderly	25 mg	6					0.500	0.50	3.00
t1/2 (hr)	Young	12.5 mg	6	7.244	41.980	7.753	3.138	6.890	4.57	12.00

Variable (SI-unit)	Age group	Treatment	n	Geometric mean	CV(%)	Arithmetic mean	SD	Median	Min	Max
		25 mg	6	7.240	40.620	7.693	2.811	7.780	4.48	11.39
		50 mg	6	7.213	57.874	8.040	3.694	8.540	3.69	12.47
		100 mg	6	5.748	39.124	6.108	2.445	5.635	3.27	10.66
	Elderly	25 mg	6	6.630	51.915	7.295	3.385	6.820	3.40	12.23
CL/F (L/hr)	Young	12.5 mg	6	152.60	32.45	158.25	40.95	167.90	82.4	206.1
		25 mg	6	163.44	26.96	168.18	42.99	173.50	119.3	211.0
		50 mg	6	150.79	60.93	174.02	109.74	117.40	93.3	361.4
		100 mg	6	136.85	66.96	159.02	92.89	135.15	65.2	291.3
	Elderly	25 mg	6	143.54	67.41	165.10	87.75	150.45	53.6	287.2
Vz/F (L)	Young	12.5 mg	6	1594.82	45.71	1730.30	789.06	1395.40	937.7	2945.2
		25 mg	6	1706.97	56.82	1906.68	948.86	1743.30	770.6	3407.0
		50 mg	6	1569.02	14.40	1582.68	231.49	1530.40	1350.8	1924.2
		100 mg	6	1135.16	57.19	1264.65	592.58	1275.60	530.8	2031.8
	Elderly	25 mg	6	1372.79	58.73	1525.72	676.59	1545.80	519.4	2501.4
CLR (mL/h)	Young	25 mg	6	7564.2	14.7	7629.2	1047.2	7915.5	5827	8697
	Elderly	25 mg	6	6225.6	12.8	6266.2	754.7	6534.5	5000	6925
Ae(0-24) (ng)	Young	25 mg	6	1120903.7	22.6	1145264.5	269659.8	1121402.0	856692	1622705
	Elderly	25 mg	6	1028421.4	57.8	1171560.0	717638.2	945426.0	588936	2514052
Ae(0-48) (ng)	Young	25 mg	6	1134484.4	21.9	1157552.7	263757.2	1141436.5	890352	1622705
	Elderly	25 mg	6	1052994.2	60.8	1212290.3	760971.8	945426.0	588936	2598322
fe(0-24) (%)	Young	25 mg	6	4.49	22.66	4.58	1.08	4.50	3.4	6.5
	Elderly	25 mg	6	4.13	57.31	4.70	2.88	3.75	2.4	10.1
fe(0-48) (%)	Young	25 mg	6	4.54	21.38	4.63	1.04	4.55	3.6	6.5
	Elderly	25 mg	6	4.22	60.12	4.85	3.04	3.75	2.4	10.4

The Cmax and AUC for naloxegol increased in young healthy volunteers in relation to dose (12.5 mg to 100 mg); increases were somewhat greater than dose proportional after the 25 mg dose; Arithmetic Cmax and AUC values in elderly following 25 mg single dose were ~ 22- 25 % higher compared to younger volunteers at the same dose. T1/2 values were comparable across doses and in young vs. elderly. There were no other marked differences in PK parameters across young versus elderly.

Summary of pharmacokinetic parameters of NKTR-118 for multiple dosing in SAD+MAD part

Variable (SI-unit)	Age group	Treatment	n	Geometric mean	CV(%)	Arithmetic mean	SD	Median	Min	Max
AUC(0-24) (hr*ng/mL)	Young	12.5 mg	6	83.04	14.29	83.73	11.83	83.40	66.6	102.2
		25 mg	6	157.75	22.74	161.08	36.16	156.75	110.8	222.0
		50 mg	6	326.23	43.09	347.98	125.34	370.35	166.2	502.5
		100 mg	6	769.09	47.27	835.57	373.10	749.95	402.4	1445.6
	Elderly	25 mg	6	230.18	41.80	247.93	116.72	217.60	146.9	474.0
AUC(0-t),ss (hr*ng/mL)	Young	12.5 mg	6	85.58	14.50	86.30	11.89	87.95	66.6	102.2
		25 mg	6	161.14	23.98	164.92	39.08	160.40	110.8	231.9
		50 mg	6	339.22	43.57	362.20	130.83	380.60	170.1	515.9
		100 mg	6	787.02	47.58	855.35	379.54	774.50	408.3	1462.2
	Elderly	25 mg	6	248.46	40.45	266.90	125.64	234.80	169.7	514.2
AUCtau,ss (hr*ng/mL)	Young	12.5 mg	6	83.04	14.29	83.73	11.83	83.40	66.6	102.2
		25 mg	6	157.75	22.74	161.08	36.16	156.75	110.8	222.0
		50 mg	6	326.23	43.09	347.98	125.34	370.35	166.2	502.5
		100 mg	6	769.09	47.27	835.57	373.10	749.95	402.4	1445.6
	Elderly	25 mg	6	230.18	41.80	247.93	116.72	217.60	146.9	474.0
AUCss (hr*ng/mL)	Young	12.5 mg	6	88.77	14.01	89.47	11.96	91.65	69.9	105.4
		25 mg	6	164.21	23.44	167.88	38.72	163.75	113.5	233.7
		50 mg	6	343.61	43.98	367.35	134.20	382.15	172.0	521.6
		100 mg	6	793.27	47.83	862.75	383.76	780.05	411.4	1469.4
	Elderly	25 mg	6	257.50	38.10	274.78	124.50	237.30	192.2	522.4
Cmax,ss (ng/mL)	Young	12.5 mg	6	18.70	32.05	19.40	5.20	20.10	10.5	25.5
		25 mg	6	52.24	30.94	54.13	14.80	55.25	31.4	70.8
		50 mg	6	104.38	55.05	117.58	69.04	99.85	55.4	249.0
		100 mg	6	416.41	73.60	494.33	316.80	398.50	148.0	1060.0
	Elderly	25 mg	6	68.58	64.87	78.47	43.22	74.40	25.6	155.0

Variable (SI-unit)	Age group	Treatment	n	Geometric mean	CV(%)	Arithmetic mean	SD	Median	Min	Max
tmax,ss (hr)	Young	12.5 mg	6					0.750	0.50	3.00
		25 mg	6					0.500	0.50	1.00
		50 mg	6					0.500	0.50	1.00
		100 mg	6					0.500	0.50	1.00
	Elderly	25 mg	6					0.500	0.50	1.50
t1/2,ss (hr)	Young	12.5 mg	6	6.686	20.676	6.803	1.381	6.815	5.17	8.78
		25 mg	6	8.377	45.282	9.082	4.140	7.410	5.78	15.69
		50 mg	6	9.678	30.772	10.068	3.232	8.390	7.61	14.71
		100 mg	6	9.827	39.416	10.435	3.939	9.590	6.33	16.00
	Elderly	25 mg	6	10.938	50.512	12.087	6.304	9.855	6.04	23.43
CL/F,ss (L/hr)	Young	12.5 mg	6	150.51	14.28	151.78	21.78	150.00	122.3	187.6
		25 mg	6	158.46	22.73	161.83	36.84	159.55	112.6	225.5
		50 mg	6	153.26	43.11	165.35	75.68	136.70	99.5	300.8
		100 mg	6	130.01	47.26	141.27	63.33	133.60	69.2	248.5
	Elderly	25 mg	6	108.59	41.83	115.28	39.55	115.65	52.7	170.2
Vz/F,ss (L)	Young	12.5 mg	6	1451.76	27.92	1496.10	387.93	1544.30	964.6	2024.4
		25 mg	6	1914.98	48.13	2097.75	1027.57	1690.35	1225.6	3804.5
		50 mg	6	2139.60	32.57	2229.53	691.86	2209.75	1340.5	3300.5
		100 mg	6	1843.68	29.43	1907.23	533.87	1982.50	1275.1	2686.5
	Elderly	25 mg	6	1713.82	95.60	2254.12	1902.06	1642.15	629.3	5751.8
CLR,ss (mL/h)	Young	25 mg	6	7578.4	13.7	7637.2	1043.7	7537.5	6517	9092
	Elderly	25 mg	6	6102.3	14.5	6154.8	871.2	6172.5	4852	7400
Ae(0-24),ss (ng)	Young	25 mg	6	1195576.7	15.2	1206864.5	179858.3	1181339.5	949502	1459254
	Elderly	25 mg	6	1404765.0	34.1	1480588.7	600222.5	1273848.0	1087140	2678065
Ae(0-48),ss (ng)	Young	25 mg	6	1206941.8	16.5	1220425.8	199494.8	1188709.0	949502	1525883

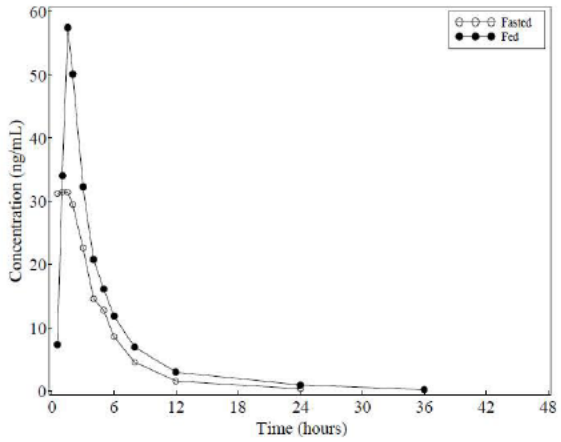
	Elderly	25 mg	6	1487847.0	34.7	1571593.2	654215.0	1331705.5	1171486	2881733
fe(0-24),ss (%)	Young	25 mg	6	4.77	14.92	4.82	0.71	4.70	3.8	5.8
	Elderly	25 mg	6	5.60	34.26	5.90	2.40	5.05	4.3	10.7
fe(0-48),ss (%)	Young	25 mg	6	4.83	16.36	4.88	0.79	4.75	3.8	6.1
	Elderly	25 mg	6	5.95	34.69	6.28	2.61	5.35	4.7	11.5
AUC(0-tau),ss(Day10)/AUC(0-24)(Day1)	Young	12.5 mg	6	1.08	35.10	1.13	0.33	1.25	0.60	1.40
		25 mg	6	1.08	27.13	1.12	0.29	1.15	0.80	1.40
		50 mg	6	1.03	21.83	1.05	0.21	1.05	0.70	1.30
		100 mg	6	1.04	23.48	1.07	0.26	1.00	0.80	1.50
	Elderly	25 mg	6	1.39	31.26	1.45	0.48	1.30	1.00	2.30
Cmax,ss(Day10)/Cmax(Day1)	Young	12.5 mg	6	1.01	23.51	1.03	0.23	1.05	0.70	1.40
		25 mg	6	1.22	57.99	1.38	0.78	1.25	0.60	2.80
		50 mg	6	0.81	44.97	0.87	0.36	0.85	0.40	1.50
		100 mg	6	1.65	59.50	1.90	1.21	1.50	0.90	4.20
	Elderly	25 mg	6	1.40	30.77	1.45	0.37	1.55	0.80	1.90
AUC(0-tau),ss(Day10)/AUC(Day1)	Young	12.5 mg	6	1.03	31.84	1.07	0.29	1.10	0.60	1.40
		25 mg	6	1.02	28.59	1.05	0.28	1.10	0.70	1.30
		50 mg	6	0.98	22.60	1.00	0.22	0.95	0.70	1.30
		100 mg	6	1.04	23.48	1.07	0.26	1.00	0.80	1.50
	Elderly	25 mg	6	1.30	39.01	1.38	0.54	1.25	0.80	2.30

Following multiple daily dosing, dose proportional increases for various AUC parameters were noted in young healthy volunteers; dose-related increases in Cmas, ss were somewhat greater than dose proportional. Compared to young healthy Japanese volunteers, Cmax and AUCtau in elderly Japanese volunteers were approximately 44- 54 % greater at steady-state. Tmax values at steady-state appeared early (median of 0.5 h). T1/2 values at steady-state varied with dose, increasing with dose increase, and in elderly volunteers, the T1/2 value at 25 mg dose were greater than that noted for young volunteers at the same dose (12 h v.s 9 h). CL/F were comparable across doses, while in elderly subjects values were somewhat lower compared to young subjects at the same dose level (115 L/h in elderly vs. 162 L/h in young subjects).

Based on AUC ratios on day 10 vs. day1, there was some accumulation in young volunteers of ~ 25 % - 35 % over the 12.5 mg to 100 mg dose range. For Cmax, the accumulation was more pronounced, ranging from 24 % to 60 % across the dose range. In elderly subjects, the accumulation following 25 mg at steady state was 31 % for both Cmax and AUC.

Food effect findings: The overall exposure to NKTR-118 (AUC) after administration of NKTR-118 in the fed state was approximately 1.5-fold greater compared to that in the fasted state and the 90% CIs were not contained within the standard bioequivalence limits (0.80 - 1.25). An increase in peak exposure (Cmax) was seen for fed compared to fasted administration (40% increase in mean ratio; upper limit of 90% CI was above the 0.80 to 1.25 range).

Geometric mean plasma concentrations (ng/mL) of NKTR-118 versus planned time following single administration of NKTR-118 under the fasted/fed condition in young healthy volunteers. Linear (upper) and Log-linear (lower) plot, 0-48 h (PK analysis set)



Pharmacokinetic variable	Comparison	Ratio	90% CI Lower	90% CI Upper
AUC (h·ng/mL)	Fed vs Fasted	1.54	1.38	1.72
$AUC_{(0\text{-}t)}$ (h·ng/mL)	Fed vs Fasted	1.51	1.38	1.66
$AUC_{(0\text{-}24)}$ (h·ng/mL)	Fed vs Fasted	1.49	1.36	1.64
C_{max} (ng/mL)	Fed vs Fasted	1.41	1.18	1.70

CI: Confidence interval

D3820C00025: A Phase I, Open-label, Randomized, Balanced, Single-dose, 2-part Study to Assess the Relative Bioavailability of NKTR-118 in 3 Formulations under Fasted (3-Way Cross-over) and Fed (2-Way Cross-over) Conditions in Male and Non-fertile Female Volunteers

Note: This study involves comparing two different oxalate formulations against the reference phase III naloxegol formulation in fed and fasted conditions. The review will focus on obtaining food-effect information for the phase III naloxegol formulation as the food-effect information for the final to-be-marketed oxalate formulation has been adequately characterized in study 00018.

Treatments:

Investigational product	Dosage form, strength, and route of administration	Manufacturer	Batch number
NKTR–118 IR Variant Fast Oxalate (Formulation 1)	Tablet, 25 mg, oral	AstraZeneca	11-000764AZ
NKTR–118 IR Variant Slow Oxalate (Formulation 2)	Tablet, 25 mg, oral	AstraZeneca	11-000441AZ
NKTR–118 (reference, (b) (4) Tablet, F13775, Formulation 3)	Tablet, 25 mg, oral	(b) (4)	17803.002

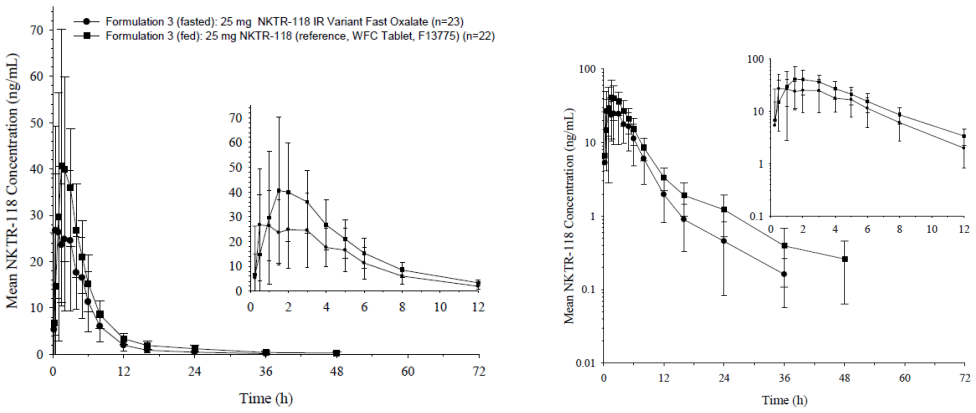
Design and objectives: This was a Phase I, open-label, randomized, balanced, cross-over, single-dose, 2-part study to investigate the relative bioavailability of 2 NKTR-118 oxalate formulations with different release characteristics (Formulations 1 and 2), compared to the Phase III formulation (Formulation 3), and to assess the effect of food on the PK of Formulation 1 and of Formulation 3.

Part A was conducted by administration of the 3 formulations under fasted conditions with a 3-way cross-over design. Each volunteer received a single oral 25 mg dose of NKTR-118 of each formulation with a wash-out period of at least 7 days between each dose. Upon completion of Period 3, the volunteers returned to the study center for Part B after a minimum of a 7-day wash-out period between doses. Only volunteers who successfully completed Part A were randomized and enrolled into Part B (Periods 4 and 5). Part B was conducted using 1 variant of the new NKTR-118 oxalate formulation (Formulation 1) and Formulation 3 (reference) administered under fed conditions with a 2-way cross-over design for each participant with a minimum of 7-day wash-out period between each dose (calculated from time of previous dose to next dose), to assess the effects of food on the PK and safety.

This review will focus on the food-effect for the phase III naloxegol formulation. The data from fed arms in Part B of the study was compared to the fasted arms in Part A. The comparison was made using an ANOVA model for each of the formulations with treatment (fed or fasted) as a fixed effect and volunteer as a random effect. The LS means for the fed and fasted treatments, LS differences between each fed treatment (test) and fasted treatment (reference) and corresponding 90% CI were estimated from the model, transformed back to original scale by exponentiation.

Results: Mean plasma naloxegol concentration-time data are shown for reference phase III formulation 3 under fed and fasted conditions:

Linear Scale **Formulation 3 (fasted vs. fed)**



Plasma concentrations of naloxegol from the phase III formulation were greater under fed conditions; similar trend was noted for the commercial naloxegol oxalate formulation (0018).

The table below summarizes the PK parameters for reference (phase III) naloxegol formulation 3 under fasted and fed conditions:

Treatment		AUC (ng*hr/mL)	$AUC_{(0-t)}$ (ng*h/mL)	C_{max} (ng/mL)	t_{max}[a] (h)	$t_{1/2\lambda z}$ (h)	CL/F L/h	V_z/F (L)
Form 3	n[a]	23	23	23	23	23	23	23
	Geo mean (CV%)	150 (47.0)	148 (47.5)	33.4 (58.8)	1.50 (0.50, 5.00)	7.74 (41.5)	166 (47.0)	1850 (55.3)
	(min, max)	(50.6, 353)	(48.7, 350)	(7.37, 80.8)		(3.84, 23.0)	(70.8, 494)	(606, 5440)
Form 3 (fed)	n[c]	21[d]	22	22	22	21[d]	21[d]	21[d]
	Geo mean (CV%)	238 (32.3)	231 (32.2)	49.5 (43.4)	1.74 (0.52, 5.00)	9.83 (35.5)	105 (32.3)	1490 (47.3)
	(min, max)	(127, 412)	(122, 408)	(23.1, 113)		(4.66, 18.6)	(60.7, 197)	(521, 4140)

Statistical comparison of the relative bioavailability information is shown below for formulation 3 (Form 3 i.e. reference or phase III naloxegol formulation):

							Comparisons	
Param	Tmt[a]	State	n	Geo LS mean	95% CI	Pair	Ratio (%)	90% CI
AUC (ng·h/mL)	Form 1	Fasted	22	161.0	(138.7, 187.0)			
		Fed	20	228.1	(195.4, 266.4)	Fed/Fasted	141.69	(129.27, 155.31)
	Form 3	Fasted	23	150.5	(127.6, 177.5)			
		Fed	21	234.0	(197.5, 277.2)	Fed/Fasted	155.47	(137.84, 175.36)
C_{max} (ng/mL)	Form 1	Fasted	22	33.26	(28.25, 39.16)			
		Fed	20	44.79	(37.68, 53.24)	Fed/Fasted	134.65	(113.81, 159.30)
	Form 3	Fasted	23	33.38	(27.16, 41.03)			
		Fed	22	48.96	(39.72, 60.35)	Fed/Fasted	146.66	(124.76, 172.42)

Data suggests that the Cmax and AUC under fed conditions were higher by 47 % and 55 % for the phase 3 (clinical trial) naloxegol formulation. In comparison, for the proposed naloxegol oxalate formulation for commercial use, food increased Cmax and AUC by ~ 30 % and 45 %, respectively (study 0018). Thus food-effect on PK appears to be greater, especially on Cmax for the clinical trial formulation; however, it should also be noted that study 00018 which evaluated food-effect for the commercial formulation was larger in size (n = 42 subjects), compared to the

current study for the clinical trial formulation (n = 22). During the phase III trials of NDA 204760 in OIC, naloxegol was administered under fasted conditions (approximately 1 h before food in the morning). In order to achieve similar exposure as in Phase 3 trials, sponsor recommends in the proposed labeling that naloxegol should therefore be dosed on an empty stomach. Dosing in the morning is recommended for patient convenience to preferably avoid bowel movements during the night.

Because the clinical trial dosing conditions and the labeled proposal for dosing are both under fasted conditions for which bioequivalence across clinical and commercial formulations appears to have been established (Study 0018- ONDQA Biopharm to confirm BE), the apparent differences noted in the food effect of the clinical vs. commercial formulations should not be clinically relevant.

D3820C00018: A Phase I, Randomized, Open-label, 3-way Cross-over Study in Healthy Volunteers to Demonstrate the Bioequivalence of the Naloxegol 25 mg Commercial and Phase III Formulations and to Assess the Effect of Food Administration on the Pharmacokinetics of the Commercial Formulation

Note: The bioequivalence of the clinical (Naloxegol) vs. commercial (Naloxegol oxalate) formulations will be reviewed by ONDQA- Biopharmaceutics group. OCP will review the food-effect aspects of the commercial formulation in this study report.

Objective: To assess the effect of food on the PK of 25 mg naloxegol oxalate commercial film-coated tablets

The assessment was part of a 3-way crossover study in 42 healthy male and female volunteers. The following three treatments were administered in a crossover manner in one of 6 sequences:

• Treatment A: Single oral administration of naloxogel film-coated IR tablet 25 mg commercial formulation under fasted conditions

• Treatment B: Single oral administration of naloxogel film-coated IR tablet 25 mg commercial formulation under fed conditions

• Treatment C: Single oral administration of naloxegol film-coated IR tablet 25 mg Phase III formulation under fasted conditions

Blood samples for PK analysis were collected at the following time-points: pre-dose (within 30 minutes prior to drug administration), 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, and 48 hours following the drug administration during each of the 3 treatment periods.

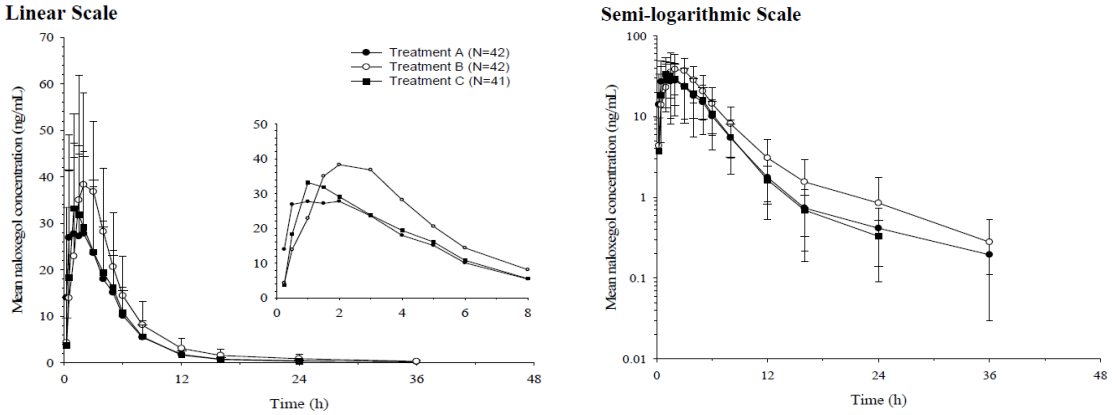
Fasted conditions: Volunteers fasted for at least 10 hours prior to the first IP administration on Day 1. A meal was given 4 hours after dosing.

Fed conditions: Volunteers had to finish a high-fat breakfast 30 minutes prior to first IP administration on Day 1. A meal was also given 4 hours after dosing.

To address the secondary objective of the study, the food effect (Treatment B: naloxegol commercial formulation under fed conditions, test) versus Treatment A (naloxegol commercial formulation under fasted conditions, reference) for the naloxegol commercial formulation was assessed for AUC, AUC(0-t), AUC(0-24), and Cmax using a linear mixed effects model with treatment, period, and sequence as fixed effects. Volunteer within sequence were included as a random effect. Geometric LS means with 95% CIs under fed and fasted conditions, the geometric LS

means ratio for fed versus fasted conditions, and the corresponding 90% CIs were provided and compared to the pre-specified interval (80.00% to 125.00%).

Results: Mean plasma-concentrations of naloxegol commercial formulation under fasted (A) and fed (B) conditions are shown in the figure below:



At a glance, concomitant dosing with food appears to have increase the peak and overall naloxegol plasma concentrations and prolonged the Tmax relative to dosing under fasted conditions. This is reflected in the mean PK data and statistical analyses below:

Treatment/statistic	AUC (ng*hr/mL)	$AUC_{(0-t)}$ (ng*h/mL)	$AUC_{(0-24)}$ (ng*h/mL)	C_{max} (ng/mL)	t_{max}[a] (h)	$t_{1/2\,\lambda z}$ (h)	CL/F L/h	V_z/F (L)
Treatment A								
n	42	42	42	42	42	42	42	42
Geo mean	145	142	140	38.3	1.00	6.99	173	1740
(CV%)	(54.5)	(54.8)	(53.8)	(54.6)	(0.23-5.02)	(59.1)	(54.5)	(59.8)
Treatment B								
n	42	42	42	42	42	42	42	42
Geo mean	210	207	202	49.7	2.00	7.72	119	1330
(CV%)	(39.6)	(39.7)	(38.4)	(44.5)	(0.50-5.00)	(42.9)	(39.6)	(51.9)

CV%: Coefficient of variation; Geo: Geometric; n: Number of healthy volunteers
Treatment A: Single oral administration of naloxegol film-coated IR tablet 25 mg commercial formulation (fasted condition).
Treatment B: Single oral administration of naloxegol film-coated IR tablet 25 mg commercial formulation (fed condition).

Statistical comparisons of food-effect (Treatments A vs. B):

						Comparisons		
Parameters	**Tmt[a]**	**State**	**n**	**Geo LS mean**	**95% CI (%)**	**Pair**	**Ratio (%)**	**90% CI (%)**
AUC (ng·h/mL)	A	Fasted	42	144.6	(126.56, 165.33)	B/A	145.09	(137.09, 153.56)
	B	Fed	42	209.9	(183.62, 239.87)			
$AUC_{(0-t)}$ (ng·h/mL)	A	Fasted	42	142.4	(124.48, 162.80)	B/A	145.72	(137.56, 154.35)
	B	Fed	42	207.4	(181.39, 237.22)			
$AUC_{(0-24)}$ (ng·h/mL)	A	Fasted	42	140.5	(123.16, 160.20)	B/A	143.60	(135.58, 152.10)
	B	Fed	42	201.7	(176.86, 230.05)			
C_{max} (ng/mL)	A	Fasted	42	38.35	(33.13, 44.39)	B/A	129.51	(115.66, 145.02)
	B	Fed	42	49.66	(42.90, 57.49)			

CI: Confidence interval(s); Geo: Geometric; IR: Immediate release; LS: Least squares; n: Number of observations; Tmt: Treatment
Results based on linear mixed effect analysis of variance model with terms for sequence, period, and treatment as fixed effects, and volunteer within sequence as a random effect.
[a] Treatment A: Single oral administration of naloxegol film-coated IR tablet 25 mg commercial formulation (fasted condition).
[a] Treatment B: Single oral administration of naloxegol film-coated IR tablet 25 mg commercial formulation (fed condition).

Data suggests that dosing with food increased Cmax and AUCt of naloxegol by ~29.50 % and ~45.7 % respectively, for the proposed commercial oxalate formulation. Tmax was prolonged and mean T1/2 was somewhat longer with food (7.72 h vs. 6.99 h); Cl/F and Vz/F both appeared to decrease when dosed with food. Thus food appears to have increased bioavailability of naloxegol.

Safety: No deaths, SAEs, or DAEs were reported in the study. The number of healthy volunteers with at least 1 AE was similar across all 3 treatment groups. The most commonly reported AEs were headache and dizziness. All AEs of headache were considered to be related to the IP administration by the Investigator. All the AEs were of mild intensity and resolved before the end of the study. Overall, no clinically relevant changes in any of the laboratory parameters, vital signs, ECG or physical examination findings were reported.

07-IN-NX002: A phase 1, double-blind, randomized, placebo-controlled, multiple-dose study to evaluate the safety, tolerability and pharmacokinetics of escalating oral doses of NKTR-118 in healthy male and female human subjects

Note: The proposed dosing regimen in OIC is 25 mg qd in the morning under fasted conditions; This particular study investigated BID regimens of an oral solution of the drug and therefore PK may not be reflective of clinical regimen; nevertheless PK linearity, proportionality, accumulation potential with a BID (worst case) regimen and safety can be assessed and therefore findings will be summarized in brief here.

Note 2: NKTR-118 is synonymous with naloxegol, NKT-10018 and PEG7-naloxol.

OBJECTIVES: The primary objective of this study was to evaluate the safety and tolerability of multiple doses of NKTR-118 in healthy male and female human subjects. The secondary objective of this study was to evaluate the pharmacokinetics of NKTR-118 and its glucuronide metabolite (NKTR-118-Glucuronide) following BID administration for 8 days.

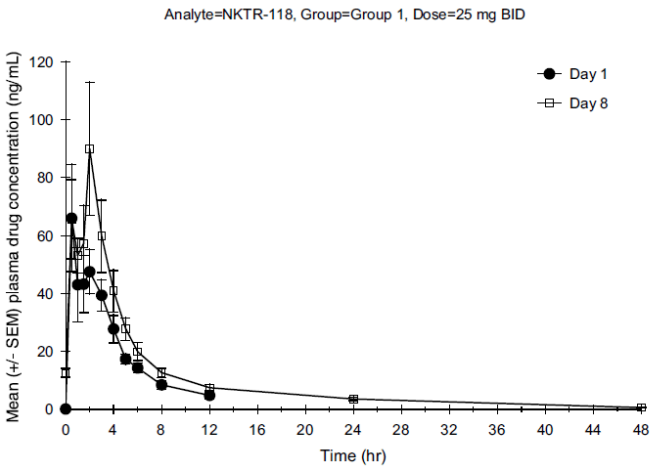
Design: a double-blind, placebo-controlled, multiple-dose, dose-escalation study in four cohorts of 8 subjects (4 females and 4 males; 18 – 65 years inclusive of age); subjects were randomized 3:1 to NKTR-118 (naloxegol) or placebo (further stratified by gender).

Doses: Doses of NKTR-118 evaluated in the four cohorts were 25 mg BID (q12h), 60 mg BID (q12h), 125 mg BID (q12h), and 250 mg BID (q12h) (50, 120, 250, and 500 mg/day), respectively. Study drug administration was twice daily during 7 consecutive days and once on the eighth day.

Assessments: Safety was assessed by monitoring adverse events, vital signs, ECG recordings, and clinical laboratory parameters. Blood and urine samples were collected for measurement of plasma and urine NKTR-118 and NKTR-118-Glucuronide concentrations, and plasma naloxone concentrations. PK blood samples for measurement of NKTR-118 and the metabolite NKTR-118-Glucuronide were obtained pre-dose and up until 12 hr post-dose on Day 1. On Days 2 to 7, PK samples were drawn pre-morning dose and pre-evening dose. On Day 8, PK samples were drawn pre-dose and up until 12 hr post-dose. Additional PK samples were drawn on Days 9 and 10 at 24 hr post last dose and at 48 hr post last dose. The following non-compartmental primary plasma pharmacokinetic (PK) parameters were derived for NKTR-118 and NKTR-118-Glucuronide: Cmax, tmax, and AUC0-12 (Days 1 and 8), λz and t1/2Z (Day 8), CLSS/F (Day 8, NKTR-118 only), VZ/F (Day 8, NKTR-118), AUC0-∞ (Day 8, NKTR-118 only), and Accumulation Ratio based on AUC0-12. Individual and mean plasma NKTR-118 and NKTR-118-Glucuronide concentration as a function of sampling time were plotted on linear and log-linear scales. Individual PK parameters were derived by non-compartmental analysis, and summarized by treatment. Attainment of steady-state, dose–proportionality, and gender comparisons were evaluated graphically.

Results: Drug absorption appears rapid after oral administration, with secondary peaks noted in several subjects in doses from 25- 125 mg. The secondary peak was more prominent at the low 25 mg dose. Naloxegol concentrations were low but quantifiable by the end of the first dosing interval (12 h). Plasma naloxegol glucuronide was below LLOQ at the low 25 mg group but was quantifiable at higher doses especially at doses 125 mg and 250 mg for up to 6 h post-dose. Variability (% CV) was high for Cmax (~ 55 %) and moderate for AUC parameters (~ 35 %).

Mean plasma naloxegol concentration-time curves are shown for day 1 and day 8 using the clinically relevant dose of 25 mg:



Primary NKTR-118 pharmacokinetic parameters (average) are shown below for day 1 and day 8:

Day 1 Dose group	(N=6) Statistic	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-12} (hr*ng/mL)	C_{max}/Dose (ng/mL/mg)	AUC_{0-12}/Dose (hr*ng/mL/mg)
25 mg q12h	n	6	6	6	6	6
	Mean	76.93	1.58	248.0	3.077	9.922
	SD	37.59	0.97	78.32	1.504	3.133
	G. Mean	69.25	NA	236.3	2.770	9.450
	CV%	54.8	NA	36.7	54.8	36.7
60 mg q12h	n	6	6	6	6	6
	Mean	242.7	0.75	531.8	4.044	8.864
	SD	112.4	0.61	239.8	1.874	3.997
	G. Mean	220.7	NA	482.5	3.679	8.041
	CV%	51.9	NA	53.6	51.9	53.6
125 mg q12h	n	6	6	6	6	6
	Mean	324.8	0.83	996.0	2.599	7.968
	SD	84.73	0.61	292.5	0.6778	2.340
	G. Mean	314.9	NA	959.6	2.519	7.677
	CV%	28.5	NA	30.9	28.5	30.9
250 mg q12h	n	6	6	6	6	6
	Mean	990.7	0.50	1974	3.963	7.896
	SD	492.8	0.00	700.9	1.971	2.804
	G. Mean	894.1	NA	1868	3.576	7.471
	CV%	52.8	NA	38.3	52.8	38.3

Day 8 Dose group	Statistic (N=6)	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-12} (hr*ng/mL)	$t_{1/2Z}$ (hr)	CL_{SS}/F (L/hr)	V_Z/F (L)	C_{max}/D (ng/mL/mg)
25 mg q12h	n	6	6	6	6	6	6	6
	Mean	96.87	1.92	363.9	9.389	77.63	1086	3.875
	SD	55.38	0.80	151.0	2.044	27.66	540.4	2.215
	G. Mean	86.15	NA	341.3	NA	73.25	973.2	3.446
	CV%	55.1	NA	39.9	NA	39.9	56.4	55.1
60 mg q12h	n	6	6	6	6	6	6	6
	Mean	288.2	1.42	961.1	10.96	66.96	1076	4.803
	SD	102.9	0.74	323.2	4.176	16.63	541.5	1.716
	G. Mean	274.0	NA	924.7	NA	64.89	967.7	4.567
	CV%	35.5	NA	29.6	NA	29.6	54.0	35.5
125 mg q12h	n	6	6	6	6	6	6	6
	Mean	489.7	0.75	1457	11.67	95.47	1587	3.917
	SD	112.8	0.61	588.6	3.111	29.89	539.1	0.9023
	G. Mean	479.0	NA	1375	NA	90.92	1483	3.832
	CV	23.4	NA	37.1	NA	37.1	46.3	23.4
250 mg q12h	n	6	6	6	6	6	6	6
	Mean	1054	0.69	2985	10.52	92.46	1437	4.217
	SD	364.1	0.30	1057	2.497	31.78	615.7	1.456
	G. Mean	1014	NA	2840	NA	88.04	1305	4.054
	CV%	29.6	NA	35.6	NA	35.6	55.3	29.6

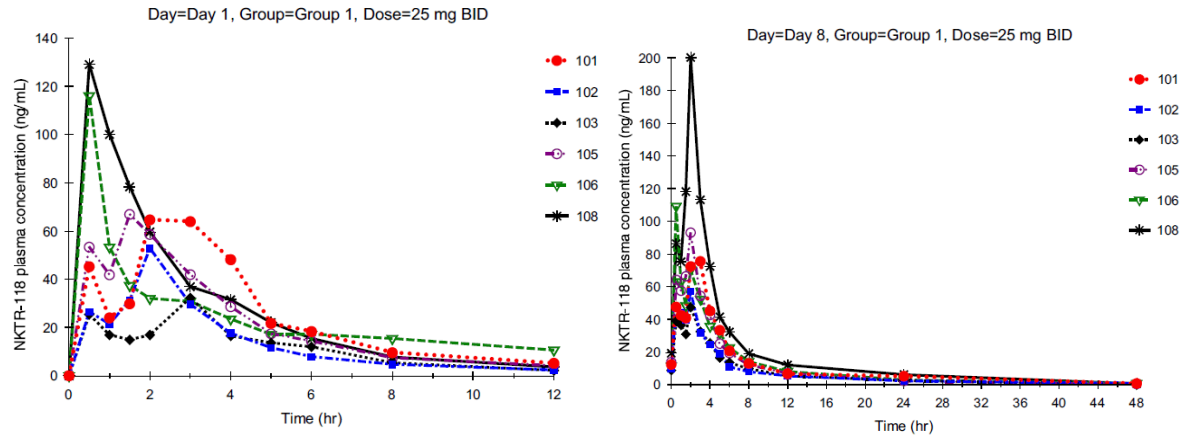
Day 8:

AUC0-t (hr*ng/mL)	n	6	6	6	6
	Mean (SEM)	461.6 (74.80)	1185 (163.9)	1873 (300.0)	3500 (475.2)
	SD	183.2	401.5	734.8	1164
	Relative SD (%)	39.69	33.88	39.23	33.26
	Geometric mean	435.5	1138	1757	3342
	Geometric CV (%)	37.67	30.46	40.79	34.55
	Median	449.1	1037	1828	3378
	Minimum, Maximum	292, 799	830, 1950	1110, 3070	1950, 5510
AUC0-inf (hr*ng/mL)	n	6	6	6	6
	Mean (SEM)	468.8 (74.54)	1220 (166.5)	1944 (309.5)	3558 (471.4)
	SD	182.6	407.9	758.0	1155
	Relative SD (%)	38.95	33.44	38.99	32.46
	Geometric mean	443.2	1172	1820	3402
	Geometric CV (%)	36.93	30.70	41.98	34.14
	Median	455.0	1081	1935	3466
	Minimum, Maximum	296, 805	841, 1980	1130, 3110	1980, 5530
t1/2Z (hr)	n	6	6	6	6
	Mean (SEM)	9.389 (0.8346)	10.96 (1.705)	11.67 (1.270)	10.52 (1.020)
	SD	2.044	4.176	3.111	2.497
	Relative SD (%)	21.78	38.11	26.65	23.75
	Geometric mean	NA	NA	NA	NA
	Geometric CV (%)	NA	NA	NA	NA
	Median	9.351	9.764	11.88	10.19
	Minimum, Maximum	6.94, 12.7	6.89, 17.1	7.42, 15.7	7.01, 14.7

CLss/F (L/hr)	n	6	6	6	6
	Mean (SEM)	77.63 (11.29)	66.96 (6.790)	95.47 (12.20)	92.46 (12.97)
	SD	27.66	16.63	29.89	31.78
	Relative SD (%)	35.62	24.84	31.31	34.37
	Geometric mean	73.25	64.89	90.92	88.04
	Geometric CV (%)	39.92	29.62	37.09	35.56
	Median	69.84	69.07	99.12	88.77
	Minimum, Maximum	39.0, 113	37.7, 84.8	49.2, 129	51.5, 147
Vz/F (L)	n	6	6	6	6
	Mean (SEM)	1086 (220.6)	1076 (221.0)	1587 (220.1)	1437 (251.4)
	SD	540.4	541.5	539.1	615.7
	Relative SD (%)	49.78	50.33	33.97	42.85
	Geometric mean	973.2	967.7	1483	1305
	Geometric CV (%)	56.36	54.01	46.28	55.33
	Median	1005	983.2	1722	1317
	Minimum, Maximum	440, 1960	509, 1950	645, 2080	521, 2140
Cmax/D (ng/mL/mg)	n	6	6	6	6
	Mean (SEM)	3.875 (0.9044)	4.803 (0.7005)	3.917 (0.3684)	4.217 (0.5945)
	SD	2.215	1.716	0.9023	1.456
	Relative SD (%)	57.18	35.72	23.03	34.53
	Geometric mean	3.446	4.567	3.832	4.054
	Geometric CV (%)	55.06	35.49	23.36	29.57
	Median	3.364	4.750	3.760	3.778
	Minimum, Maximum	1.89, 8.00	2.92, 7.80	2.74, 5.30	3.14, 7.12

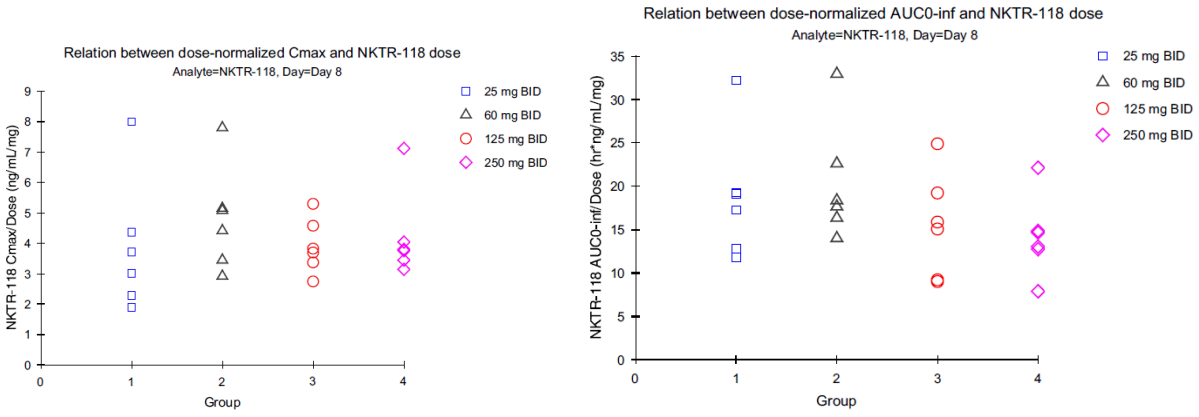
AUC0-t/D (hr*ng/mL/mg)	n	6	6	6	6
	Mean (SEM)	18.46 (2.992)	19.75 (2.732)	14.98 (2.400)	14.00 (1.901)
	SD	7.328	6.691	5.879	4.656
	Relative SD (%)	39.69	33.88	39.23	33.26
	Geometric mean	17.42	18.97	14.06	13.37
	Geometric CV (%)	37.67	30.46	40.79	34.55
	Median	17.96	17.28	14.63	13.51
	Minimum, Maximum	11.7, 32.0	13.8, 32.5	8.89, 24.6	7.81, 22.1
AUC0-inf/D (hr*ng/mL/mg)	n	6	6	6	6
	Mean (SEM)	18.75 (2.982)	20.33 (2.775)	15.55 (2.476)	14.23 (1.886)
	SD	7.304	6.799	6.064	4.619
	Relative SD (%)	38.95	33.44	38.99	32.46
	Geometric mean	17.73	19.53	14.56	13.61
	Geometric CV (%)	36.93	30.70	41.98	34.14
	Median	18.20	18.02	15.48	13.86
	Minimum, Maximum	11.8, 32.2	14.0, 33.0	9.02, 24.9	7.90, 22.1

Individual plasma c vs. t. plots at the 25 mg dose show considerable variability in peak concentrations across individuals:



Dose proportionality: Based on dose normalized Cmax and AUC parameters, there was considerable fluctuation of these values on day 1 across the doses evaluated. The fluctuation was less prominent on day 8, but nevertheless the dose-normalized exposure parameters tended to be somewhat smaller at the higher doses. Large Vz/F suggested substantial distribution outside the plasma compartment. Terminal elimination half-life ranged from 9.5- 11.5 h across doses and did not exhibit a definite trend across doses.

Scatter plots of DN-Cmax or AUC0-12 vs. dose group on day 8 are presented for parent drug:



Additionally, scatter plots by gender showed that DN-Cmax, and DN-AUC0-12 values for males and females were similar, both on Day 1 and Day 8, indicating the absence of NKTR-118 pharmacokinetic difference with gender.

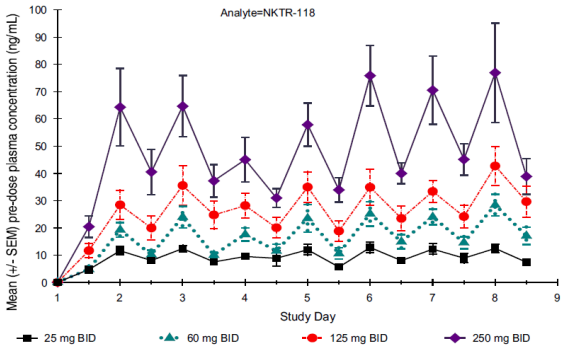
Accumulation with the BID dosing is summarized below and the ratios based on Cmax and AUC appeared independent of dose:

APPEARS THIS WAY ON ORIGINAL

Analyte	Parameter	Statistics	25 mg BID (N=6)	60 mg BID (N=6)	125 mg BID (N=6)	250 mg BID (N=6)
NKTR-118	AUC(0-12)	n	6	6	6	6
		Mean (SEM)	1.461 (0.1018)	1.998 (0.2688)	1.478 (0.1606)	1.543 (0.1203)
		SD	0.2493	0.6585	0.3935	0.2947
		Relative SD (%)	17.06	32.96	26.63	19.10
		Geometric Mean	1.445	1.917	1.433	1.520
		90% confidence interval for the geometric mean	[1.218 , 1.713]	[1.387 , 2.648]	[1.072 , 1.915]	[1.247 , 1.854]
		Geometric CV (%)	16.37	31.53	28.21	19.07
		Median	1.393	1.719	1.474	1.525
		Minimum, Maximum	1.20, 1.89	1.44, 3.05	0.929, 2.07	1.18, 2.01
	Cmax	n	6	6	6	6
		Mean (SEM)	1.264 (0.09777)	1.302 (0.1725)	1.618 (0.2713)	1.175 (0.1350)
		SD	0.2395	0.4226	0.6646	0.3307
		Relative SD (%)	18.95	32.47	41.07	28.14
		Geometric Mean	1.244	1.242	1.521	1.134
		90% confidence interval for the geometric mean	[1.014 , 1.527]	[0.8655 , 1.781]	[1.040 , 2.225]	[0.8265 , 1.555]
		Geometric CV (%)	19.71	35.43	39.06	30.80
		Median	1.277	1.278	1.514	1.129
		Minimum, Maximum	0.940, 1.55	0.729, 1.90	0.889, 2.87	0.697, 1.55

Glucuronide concentrations were below detectable in all subjects at the clinically relevant dose of 25 mg, while they increased in relation to dose at the higher doses.

Trough concentrations were higher just prior to the morning dose of naloxegol compared to the trough levels measured prior to the evening dose. This was consistently noted across all doses. However, given that the sponsor is proposing a once-daily regimen (unlike BID regimen used in this study) the diurnal variability may not be relevant. The plot below summarizes the average trough levels at each of the dose levels given BID:



Plasma naloxone concentrations were all below the lower limit of quantitation (0.25 ng/mL). These plasma concentrations were measured to verify that the NKTR-118 administration dose not result in systemic exposure to naloxone.

Conclusions: Study evaluated PK of naloxegol and glucuronide metabolite after 25, 60, 125 and 250 mg BID doses in healthy male and female volunteers. Drug absorption was rapid after oral dosing; secondary peaks were noticeable at lower doses prolonging the apparent Tmax. Trough levels fluctuated widely with the BID dosing regimen, with troughs after the PM doses tending to be higher than the troughs after the AM doses probably due to food-effect on PK. Some accumulation was noted on day 8 that was independent of dose; steady-state appeared to have reached within couple of doses based on average trough levels. Dose proportionality couldn't be definitively established as higher doses tended to have lower dose normalized Cmax and AUC compared to the two lower doses; T1/2 was approximately 9.5-11.5 h across the doses evaluated. The NKTR-118 glucuronide metabolite was below detectable limits at the clinically relevant dose of 25 mg while it was quantifiable at higher doses. A large volume of distribution suggests extensive distribution outside the plasma compartment. No marked differences in exposures were noted across genders. Variability in exposures ranged from 35- 55 % across parameters.

Report 07-IN-NX003- A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Multiple-Dose, Dose-Escalation Study to Evaluate the Efficacy, Safety and Tolerability of NKTR-118 in Patients with Opioid-Induced Constipation (OIC)

Primary Objective

 To evaluate the efficacy of NKTR-118 at various dose levels, *with efficacy defined as the change from baseline in the number of spontaneous bowel movements (SBMs) per week*

Secondary Objectives

 The main secondary objective was to evaluate the safety and tolerability of NKTR-118, thereby enabling identification of an effective dose that preserves opioid-conferred analgesia

 Delineate dose-response for NKTR-118 across a range of underlying opioid doses, with response defined as the change from baseline in SBMs/week

 Characterize the PK of NKTR-118 in patients

Study design: This was a multicenter, international, randomized, double-blind, placebo-controlled, multiple-dose, dose-escalation, 4-cohort study of the efficacy, safety, and tolerability of NKTR-118 in patients with documented OIC. Patients with confirmed OIC were randomized and entered a 1-week on-study, single-blind placebo run-in period, followed by 4 weeks of randomized double-blind treatment with NKTR-118 or placebo.

This study planned to enroll up to 4 sequential dose cohorts comprising approximately 240 patients. Approximately 16 patients per cohort were planned for inclusion in the PK substudy. The doses of NKTR-118 for Cohorts 1, 2, 3, and 4, respectively, were originally scheduled to be 5 mg, 25 mg, 50 mg, and 100 mg QD; however, based upon the safety review of safety data from the 50 mg data, the 100 mg qd dose was not evaluated. A 4 % naloxegol oral solution was used in this study.

Patients were randomized within each cohort in a 1:1 ratio (active: placebo). Randomization was stratified based on total daily opioid dose at baseline. The patient's daily maintenance opioid dose was converted to the equivalent dose in mg for orally administered morphine, expressed as morphine equivalent units (MEU) (low stratum, 30 to 100 MEU; high, > 100 to 1000 MEU).

Efficacy assessments: The primary efficacy variable was the change from baseline in SBMs/week at Visit 6 and defined as SBMs/week during the first week of double-blind study medication (between Visit 4 and Visit 6) minus baseline SBMs/week. Baseline was defined as the average SBMs/week during the 2-week OIC screening period.

Pharmacokinetic assessments: Plasma naloxegol and glucuronide were assessed from samples taken during day 1 of weeks 1, 2, 3, and 4 of the study period. Approximately 16 patients per cohort were to be enrolled at investigational PK sites in the PK substudy, in which serial blood (~10 mL each) samples were collected at the following timepoints: at predose, and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 18, and 24 (within 0.5 hours before second dose) hours post-first randomized dose; at pre-dose for two weekly visits in between; and at predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, and 48 hours post-dose for the last dose. PK parameters such as Cmax, Tmax, AUC24, AUC48, T1/2z, CLss/F, Vz/F and accumulation ratios were calculated. Concentrations of naloxone were also evaluated in plasma samples.

Urine collection for the PK substudy occurred at Week 2 (Visit 4) over the 0-12 and 12-24 hour intervals following the first dose and at Week 6 (Visit 9) over the 0-12, 12-24, 24-36, and 36-48 hour intervals following the last dose.

Sparse Pharmacokinetic Sampling (Non-Pharmacokinetic Substudy): For all patients who did not participate in the serial blood and urine sampling, 5 blood samples (~10 mL each) were obtained as follows: at pre-dose before the first dose of randomized treatment; at pre-dose for two weekly visits after; and at pre-dose before the last dose and between 0.25 hours (15 minutes) and 6 hours after the last dose.

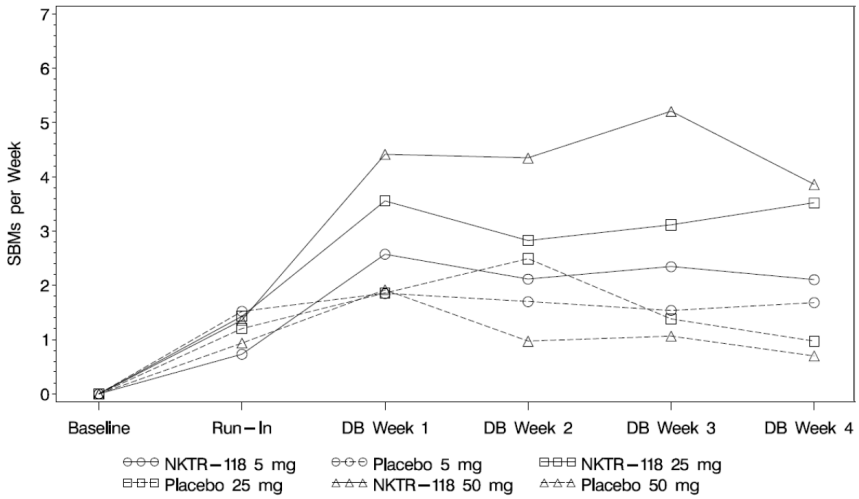
Results:

Efficacy outcomes: Primary efficacy endpoint:

Change from Baseline in Spontaneous Bowel Movements Per Week: MITT Population

Mean (SD)	**Placebo** **N = 31**	**5 mg QD** **N = 31**	**Placebo** **N = 27**	**25 mg QD** **N = 29**	**Placebo** **N = 37**	**50 mg QD** **N = 30**
Run-in	1.5 (2.0)	0.7 (1.9)	1.2 (2.2)	1.4 (1.6)	0.9 (2.2)	1.4 (2.1)
Week 1	1.8 (2.4)	2.6 (3.6)	1.9 (2.5)	3.6 (2.3)	1.9 (5.2)	4.4 (3.8)
Week 2	1.7 (1.7)	2.1 (2.7)	2.5 (3.7)	2.8 (2.1)	1.0 (1.7)	4.3 (3.6)
Week 3	1.5 (2.3)	2.3 (3.2)	1.4 (1.9)	3.1 (2.9)	1.1 (2.1)	5.2 (4.4)
Week 4	1.7 (2.4)	2.1 (3.0)	1.0 (2.2)	3.5 (2.3)	0.7 (1.9)	3.9 (3.9)
Weeks 1-4	*1.7 (1.9)*	*2.3 (2.9)*	*1.7 (2.2)*	*3.2 (2.0)*	*1.2 (2.0)*	*4.6 (3.4)*

Dose Response for Change from Baseline in Spontaneous Bowel Movements Per Week:



Within each cohort, the change from baseline in SBMs per week were greater for the naloxegol treatment group, compared to placebo, with dose related increases in change from baseline noted at all four weeks. The p-value relative to placebo was significant for the 25 mg qd (except at week 2) and the 50 mg qd doses but not the 5 mg qd dose of naloxegol. For all weeks combined, p-value < 0.05 was noted for the 25 mg and 50 mg qd doses of naloxegol.

In addition to the primary efficacy analysis, change in weekly SBM frequency was evaluated:

Frequency of Spontaneous Bowel Movements Per Weeks 1-4 During Double-Blind Treatment: MITT Population

	5 mg QD		25 mg QD		50 mg QD	
	Placebo N=31	NKTR-118 N=31	Placebo N=27	NKTR-118 N=29	Placebo N=37	NKTR-118 N=30
MITT Total Population						
SBMs/Weeks 1-4, N	27	29	27	28	35	24
Mean (SD)	3.2 (2.1)	4.2 (2.7)	2.9 (2.3)	4.6 (2.4)	2.6 (1.8)	6.2 (3.6)
Median (Q1, Q3)	3.0 (1.8, 4.0)	3.5 (2.8, 4.4)	2.3 (1.3, 3.8)	4.6 (2.9, 6.2)	2.6 (1.3, 3.4)	5.3 (4.0, 6.5)
Min, Max	0.0, 10.4	1.1, 14.3	0.0, 10.0	0.5, 9.3	0.3, 9.0	2.3, 17.5
MITT Low-Baseline Opioid Stratum						
SBMs/Weeks 1-4, N	9	12	13	11	17	12
Mean (SD)	4.7 (2.7)	3.8 (2.6)	3.3 (3.1)	6.0 (2.4)	2.7 (2.4)	5.9 (3.9)
Median (Q1, Q3)	3.8 (3.0, 5.2)	3.4 (2.1, 4.4)	2.9 (1.0, 3.8)	6.0 (4.4, 8.0)	2.3 (0.5, 4.1)	4.8 (4.0, 6.4)
Min, Max	1.5, 10.4	1.1, 9.3	0.3, 10.0	1.3, 9.3	0.3, 9.0	2.3, 17.5
MITT High-Baseline Opioid Stratum						
SBMs/Weeks 1-4, N	18	17	14	17	18	12
Mean (SD)	2.5 (1.3)	4.4 (2.9)	2.5 (1.4)	3.8 (1.9)	2.4 (1.0)	6.4 (3.5)
Median (Q1, Q3)	2.6 (1.3, 3.6)	3.5 (3.1, 4.8)	2.3 (1.6, 3.4)	4.4 (2.5, 5.0)	2.7 (1.3, 3.1)	5.5 (3.9, 7.8)
Min, Max	0.0, 4.5	1.9, 14.3	0.0, 4.8	0.5, 6.5	0.5, 4.3	3.0, 13.5

Min, minimum; max, maximum.

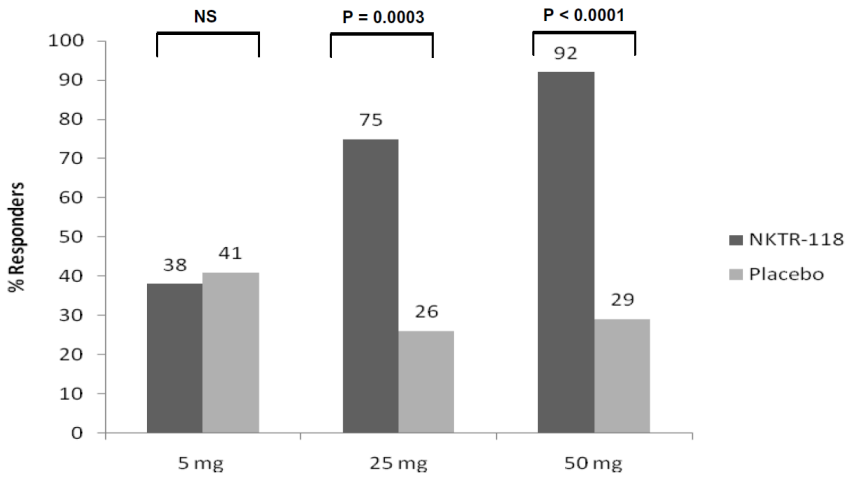
Mean number of SBMs per week increased with dose: 4.2, 4.6 and 6.2 at 5, 25 and 50 mg qd.

Secondary efficacy outcomes:

Median time to first laxation (hours) for each dose cohort is presented below; this value was significant for naloxegol relative to placebo for the 25 mg and 50 mg qd dose groups; median time to first laxation was 6.2 h, 6.6 h and 2.9 h for the 5, 25 and 50 mg qd doses.

	5 mg QD		25 mg QD		50 mg QD	
	Placebo N=31	NKTR-118 N=31	Placebo N=27	NKTR-118 N=29	Placebo N=37	NKTR-118 N=30
Percentiles						
25th	5.6	3.5	21.0	2.0	10.9	1.1
Median	28.2	6.2	48.6	6.6	44.9	2.9
75th	51.4	69.2	72.4	25.0	154.4	22.9
P value[3]		0.6324		0.0012		0.0016

Sponsor's post-hoc analysis of proportion of responders (those with increase of at least 2 SBMs over baseline) suggests significant increase with the 25 mg qd and 50 mg qd dose groups:



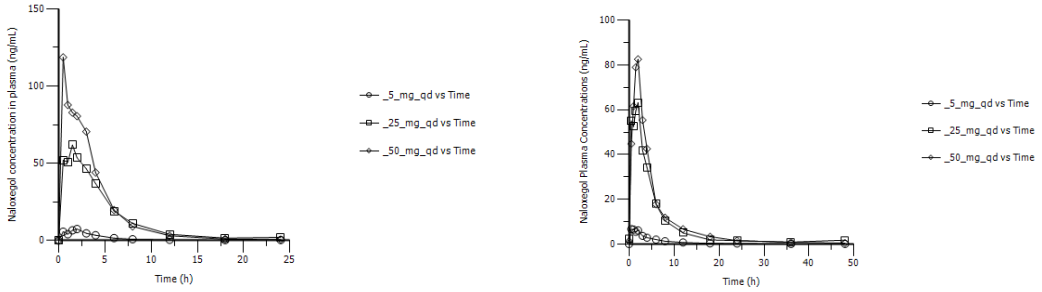
PK results: In the PK substudy, after exclusions, there were 5, 12, and 5 patients with evaluable PK data in the 5, 25, and 50 mg dose groups, respectively, within the PK analysis population. Naloxegol-Glucuronide was undetectable in plasma (LLOQ 0.5 ng/mL) except for patients in the 50 mg dose group, where concentrations were approximately 1 ng/mL or less throughout the study. Plasma naloxone concentrations were below the 0.25 ng/mL LLOQ in all samples from both PK populations. PK data [Mean (%CV)] following the first and last doses in OIC patients in this phase 2 study are shown below. Mean data suggests greater than dose proportional increases in Cmax and AUC between 5 mg and 25 mg doses; the increase from 25 to 50 mg appears to be less than dose proportional on day 1; Tmax values were comparable across doses.

At steady-state, the trends remained; no evidence of accumulation was noted following daily dosing. The T1/2 values in the patient population appeared greater on average, compared to those noted in healthy volunteer studies. % CV ranged from 22 – 52 % across doses. Steady-state appears to have been achieved in patients by day 7 based on trough data.

Day	Dose (mg)	N	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{(0-24)}$ (hr*ng/mL)	$T_{1/2}$ (hr)
1	5	5	1.7 (84.7)	9.1 (52.2)	34.01 (48.8)	NC
	25	12	1.5 (61.1)	70.6 (42.3)	327.7 (47.7)	NC
	50	5	1.5 (91.3)	123.7 (36.3)	426.8 (22.1)	NC
28	5	4	1.5 (81.7)	8.0 (49.2)	39.0 (23.1)	17.4 (8.3)
	25	9	1.4 (43.9)	81.1 (45.7)	334.8 (51.4)	14.1 (4.9)
	50	4	1.6 (101.7)	100.0 (41.9)	403.6 (36.7)	20.3 (10.3)

Reviewers analyses - NCA and plots using mean concentration-time data:

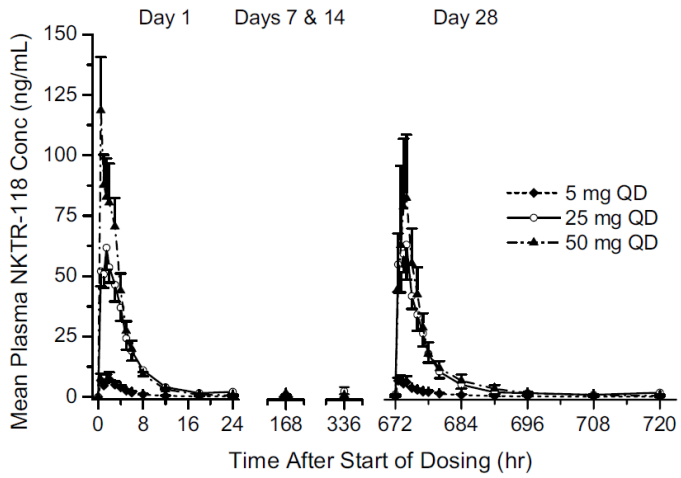
	5 mg day 1	25 mg day 1	50 mg day 1	5 mg at SS	25 mg at SS	50 mg at SS
Tmax	2.00	1.50	0.50	0.50	2.00	2.00
Cmax	7.44	61.78	118.58	6.82	63.14	82.45
AUClast	33.98	330.90	431.48	45.15	368.00	429.87
AUCall	33.98	330.90	431.48	45.15	368.00	429.87
AUCINF_obs	36.49	343.18	434.28	48.15	393.43	443.93
HL_Lambda_z	5.29	4.09	2.90	10.38	9.32	16.25



Metabolite profiling was done in plasma and urine and no metabolite (out of 16 total) was > 10 % in abundance relative to parent drug after 28 days of dosing, suggesting the absence of major metabolites. Naloxegol glucuronide was below detection for doses up to 25 mg qd or was found at very low concentrations of 1 ng/mL at the highest dose evaluated 50 mg qd. Based on metabolite comparisons between days 1 and 28, it doesn't appear that any metabolite accumulates to a significant extent.

Metabolites	Urine - Mean±SD (n)				Plasma - Mean±SD (n)	
	Collection Period 0-12 hr		Collection Period 12-24 hr		Collection Period 0-4 hr	
	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
M-417	3.2 (1)	1.7 (1)	ND	ND	ND	ND
M-461	0.8±0.8 (5)	1.3±1.1 (3)	7.3 (2)	3.4±3.8 (3)	ND	ND
M-475	2.0±1.9 (5)	0.8±0.3 (3)	4.3±1.8 (5)	2.2±1.6 (5)	ND	ND
M-505	1.4±0.8 (11)	1.3±1.3 (11)	1.8±1.2 (4)	1.7±1.9 (6)	3.7±0.4 (4)	3.9 (1)
M-519	1.1±1.8 (7)	0.4±0.3 (7)	4.6±2.5 (5)	2.4±1.4 (5)	ND	ND
M-549	2.0±1.4 (11)	1.5±1.0 (11)	2.9±2.2 (7)	2.4±0.9 (7)	ND	ND
M-563	0.9±1.0 (8)	0.6±0.3 (6)	2.2±1.1 (4)	2.0±1.1 (4)	ND	ND
M-593	1.2±1.2 (11)	0.5±0.3 (8)	2.3±2.6 (6)	1.3±0.7 (9)	ND	ND
M-607	0.5±0.4 (8)	0.4±0.4 (6)	1.3±0.6 (7)	2.8±0.9 (4)	ND	ND
M-611	1.4±1.5 (10)	1.0±1.2 (10)	4.2±3.5 (8)	2.8±1.4 (11)	4.7±2.4 (12)	6.0±1.6 (13)
M-627	0.6 (1)	ND	ND	ND	ND	ND
M-637	0.8±0.8 (3)	0.2 (1)	ND	ND	ND	ND
M-651	0.2±0.2 (11)	0.5±0.5 (9)	1.0±0.9 (10)	2.1±1.1 (5)	ND	ND
M-667	0.7±0.6 (10)	0.8±0.5 (8)	2.1±1.5 (7)	1.7±1.1 (10)	ND	ND
M-770	0.5±0.3 (4)	0.6±0.5 (6)	0.8 (1)	0.9 (1)	ND	ND
M-827	ND	0.1 (1)	ND	ND	ND	ND

ND=not detected.

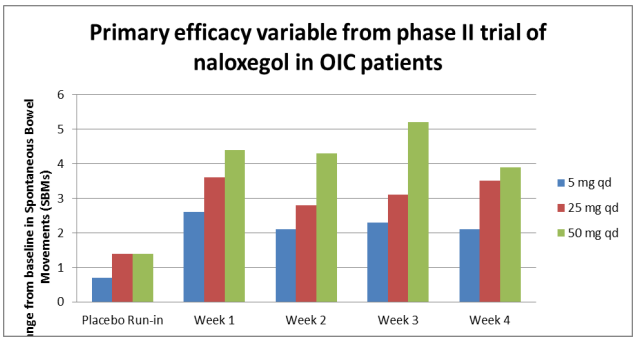


Safety: Sixteen patients in Cohort 1 (5 mg), 16 patients in Cohort 2 (25 mg) and 23 patients in Cohort 3 (50 mg) experienced at least 1 TEAE that was assessed as being causally related to the study drug. The majority of study drug (NKTR-118) related TEAEs reported within all 3 cohorts were in the System Organ Class (SOC) of GI disorders with diarrhea, abdominal pain, and nausea accounting for the most frequent TEAEs. Of the 7 SAEs, 4 were experienced by patients in the NKTR-118 arm and 3 were reported in the placebo group. Of the 4 SAEs experienced by NKTR-118 patients, 1 SAE reported in Cohort 3 (50 mg) was assessed as being related to the study drug NKTR-118. This study drug-related treatment-emergent SAE of abdominal cramping was experienced by the patient shortly after administration of the first dose of the study drug. Following review of 8 AEs of special interest and the aggregate safety data from patients in Cohort 3 (50 mg), the DESC recommended against dose escalation to a fourth dose cohort at 100 mg, as GI intolerability would likely lead to a significant number of patients terminating from treatment early. Mean bisacodyl rescue medication use was numerically lower for the NKTR-118 arms of Cohort 2 (25 mg) and Cohort 3 (50 mg) vs placebo at all postdose timepoints; however, a statistical comparison was not done. Opioid withdrawal was found to be greater with the 50 mg qd group particularly on day 1 compared to placebo, but this was primarily due to greater frequency of GI adverse events (abdominal pain, diarrhea and nausea); without inclusion of GI events, the incidence of opioid withdrawal events were no longer significant between any dose group vs. placebo. Sponsor also notes that based on pain scores and increase in opiate use, there appears to be no reversal or reduction of opioid-mediated analgesia at any of the dose groups evaluated in this trial.

Additional data and plots for dose-response information in phase 2 trial:

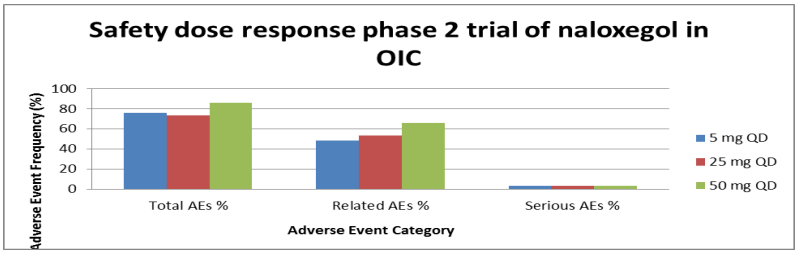
Efficacy:

	5 mg qd	25 mg qd	50 mg qd
Placebo Run-in	0.7	1.4	1.4
Week 1	2.6	3.6	4.4
Week 2	2.1	2.8	4.3
Week 3	2.3	3.1	5.2
Week 4	2.1	3.5	3.9



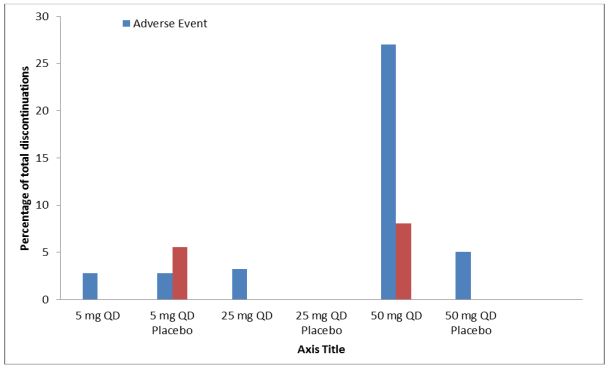
Safety dose response phase 2 (%)

	Total AEs	Related AEs	Serious AEs
5 mg QD	75.8	48.5	3.0
25 mg QD	73.3	53.3	3.3
50 mg QD	85.7	65.7	2.9



Data shown as % of the total discontinuations

	5 mg QD	5 mg QD Placebo	25 mg QD	25 mg QD Placebo	50 mg QD	50 mg QD Placebo
Adverse Event	2.78	2.78	3.25	0.00	26.99	5.08
Consent withdrawn	0.00	5.56	0.00	0.00	8.09	0.00
Opioid Withdrawal	2.78	0.00	0.00	0.00	0.00	0.00



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDHYA K APPARAJU
05/14/2014
Part 2 of Naloxegol review- Clinical Pharmacology Individual Study Reviews

SUE CHIH H LEE
05/14/2014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**204760**	**Brand Name**	**TBD**
OCP Division (I, II, III, IV, V)	**DCP III**	**Generic Name**	**Naloxegol Oxalate**
Medical Division	**DGIEP**	**Drug Class**	**Peripherally Acting mu-opioid receptor antagonists (PAMORA)**
OCP Reviewers	**Sandhya Apparaju, Ph.D. Elizabeth Shang, Ph.D.**	**Indication(s)**	**Treatment of Opioid-induced Constipation (OIC) in adults with chronic non-cancer pain**
OCP Team Leader	**Sue Chih Lee, Ph.D.**	**Dosage Form**	**Film coated Tablets (IR)**
Pharmacometrics Reviewer Pharmacometrics signatory/TQT review PBPK Team Leader	**Dr. Justin Earp Dr. Kevin Krudys Dr. Ping Zhao**	**Dosing Regimen**	**25 mg once daily**
Date of Submission	**September 16, 2013**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**05/16/2013**	**Sponsor**	**AstraZeneca Pharmaceuticals LP**
Medical Division Due Date	**07/16/2013**	**Priority Classification**	**Standard**
PDUFA Due Date	**09/16/2013**		

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**	**51 (Total)**		**13 phase 1 1 TQT 1 Phase 2 1 PBPK 3 population PK/E-R 5 *in vivo* metabolic profiling 10 bioanalytical reports 12 *in vitro* studies 5 phase 3**
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	10		
I. Clinical Pharmacology				
Mass balance:	**X**	2		^{14}C-labeled drug; MB study; metabolite profiling report
Isozyme characterization:	**X**			
Blood/plasma ratio:	**X**			
Plasma protein binding:	**X**			
Pharmacokinetics (e.g., Phase I) -	**X**			
Healthy Volunteers-				
single dose:	**X**	1		PK and PD
multiple dose:	**X**	2		Caucasians, Japanese

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Patients-				
single dose:				
multiple dose:	**X**			
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	4		In vivo studies with Quinidine, ketoconazole, rifampin, diltiazem
In-vivo effects of primary drug:				
In-vitro:	**X**	12		In vitro ADME, DDI studies
Subpopulation studies -				
ethnicity:	**X**	5		5 phase 3 studies; pop PK covariate
gender:	**X**			pop PK covariate
pediatrics:				
geriatrics:	**X**			pop PK covariate; PK in elderly also evaluated as part of Japanese PK study
renal impairment:	**X**	1		PK and safety in Control *vs.* Moderate, Severe, ESRD RI
hepatic impairment:	**X**	1		PK and safety in control vs. HI (severe not studied)
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	2		Phase 1 PK/PD; TQT study
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**X**			Phase II and Phase III trials
II. Biopharmaceutics	**X**	3		BA/BE, food effect studies
Absolute bioavailability				
Relative bioavailability -				
solution as reference:	**X**	1		
alternate formulation as reference:	**X**	1		
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	1		Clinical vs. To-be-marketed; ONDQA Biopharm will review report, OSI inspection & analytical assays
replicate design; single / multi dose:				
Food-drug interaction studies	**X**			Food effect evaluated as part of BA/BE studies; pivotal BE and Japanese PK study
Bio-waiver request based on BCS				
BCS class				Proposed to be a Class III drug
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies	X	5		1 PBPK report; 4 metabolite profiling reports
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**X**			
Literature References	**X**			
Total Number of Studies	**X**	**51**		

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	NA			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. The proposed metabolism of Naloxegol, a pegylated product is described as formation of partially shortened PEG chain products. Address the potential for the formation and systemic accumulation of ethylene glycol, diethylene glycol as well as their toxic metabolites as by-products of this metabolism.
2. We notice that in the mass balance study the ^{14}C-radio label is located on the PEG side chain rather than on naloxone moiety. You have noted in your metabolite profiling report that "No radiochromatographic peak corresponds to naloxone or naloxol indicating that, if formed, these would represent less than 1% of unchanged NKTR-118". Given the position of the radiolabel, address how you have ensured that no naloxone has formed during in vivo studies in humans.

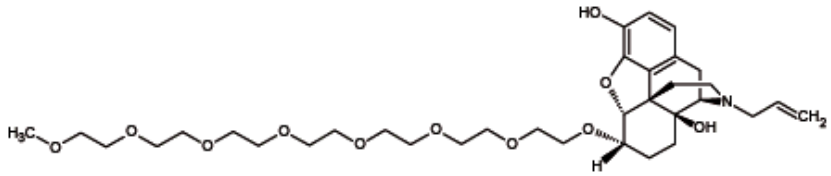
Sandhya Apparaju, Ph.D.; Elizabeth Shang, Ph.D.

Reviewing Clinical Pharmacologists Sue Chih Lee, Ph.D.	Date
Team Leader/Supervisor	Date

Clinical Pharmacology filing memo:

Sponsor is developing Naloxegol Oxalate, a pegylated derivative of naloxone for the treatment of opioid-induced constipation (OIC) in non-cancer pain. Naloxegol is a peripherally acting mu-opioid receptor antagonist (PAMORA) and is expected to alleviate GI related side effects of opioid drugs i.e. constipation, without affecting the CNS effects i.e. analgesia.
The pegylation is expected to reduce drug's passive uptake and also render it a substrate of P-gp, thus reducing CNS permeability. The formulation proposed is an immediate release film coated tablet; the proposed dose in most patients is 25 mg once daily, with dosage adjustments in place for patients on moderate CYP3A4 inhibitors. The proposed trade name is MOVANTIG (pending approval).

NKTR-118



NDA includes 14 phase 1 studies (single dose and multiple dose PK, PD, food-effect, BA/BE, including clinical vs. To-Be-Marketed formulation, Thorough QT, effect of intrinsic factors (hepatic, renal impairment, ethnicity), effect of extrinsic factors (ketoconazole, rifampin, quinidine, diltiazem), 5 studies characterizing metabolite profile in samples from phase 1 studies,1 phase II study for dose-finding, 5 phase III studies, as well as 12 in vitro studies for evaluating ADME and DDI potential. Additionally, validation and assay reports for bioanalysis of drug and other analytes are included. Datasets are provided in appropriate format. Study reports, Bioanalytical validation and assay reports could be located. Draft labeling has been included with Clinical Pharmacology sections populated and annotated.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

List of Clinical Pharmacology studies:

Study Phase and Identifier	Objectives	Design & type of control	Test products, Dosage regimen	No. of subjects rand/treated/ diagnosis of patients	Duration of treatment	Assessments
Healthy subject pharmacokinetic (PK) and initial tolerability studies						
Phase I **05-IN-OX001** Single ascending dose study	Evaluate safety, tolerability, potential antagonistic effects of NGL on morphine-induced delay in orocecal transit time, and potential antagonistic effects of NGL on morphine-induced pupil constriction; and the PK of NGL and it glucuronide metabolite	Double-blind, randomised, placebo-controlled, 2-treatment crossover, with 8 separate dose cohorts	Individual dose cohorts received 2 treatments: 8 mg, 15 mg, 30 mg, 60 mg, 125 mg, 250 mg, 500 mg, or 1000 mg NGL via solution and placebo solution, separated by 5 to 7 day washout periods	48 healthy volunteers (6 for each dose cohort)	1 single-dose treatment day	**Safety**: AEs, BP, pulse rate, oral temperature, physical examination, ECG, O_2 saturation, hematology, clinical chemistry, urinalysis **PD**: Orocecal transit time, pupil diameter **PK NGL**: C_{max}, T_{max}, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$, AUC extrapolated, CL, Plasma $t_{1/2}$ for NGL and NGL glucuronide **PK Morphine**: C_{max}, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$ for morphine, morphine-3-glucouronide and morphine-6-glucuronide with and without NGL

Study Phase and Identifier	Objectives	Design & type of control	Test products, Dosage regimen	No. of subjects rand/treated/ diagnosis of patients	Duration of treatment	Assessments
Phase I **07-IN-NX002** Multiple ascending dose study	Evaluate safety and tolerability of multiple doses of NGL and PK of NGL and its glucuronide metabolite, with twice daily dosing for 7.5 days	Double-blind, randomised, placebo-controlled, 2 treatment, parallel group, with 4 separate dose cohorts	Individual dose cohorts received 25 mg, 60 mg, 125 mg, or 250 mg NGL or placebo, twice daily for a period of 7. 5 day	32 healthy volunteers (8 in each dose cohort)	7.5 days: twice daily dosing on days 1-7 + once on day 8	**Safety**: AEs, BP, pulse rate, oral temperature, body weight, physical examination, ECG, hematology, clinical chemistry, urinalysis **PK** NGL & NGL glucuronide: C_{max}, T_{max}, $AUC_{(0\text{-}12)}$ (Days 1 & 8); λZ & $t1/2z_{(Day\ 8)}$; CLss/F, Vz/F, $AUC_{(0\text{-inf})}$ (Day 8, NGL only); Accumulation ratio based on $AUC_{(0\text{-}12)}$
Phase I **D3820C00001** ^{14}C absorption, distribution, metabolism and excretion study	To characterize the absorption, distribution, metabolism and excretion of a single oral dose of $^{(14)}C$-NGL in healthy male volunteers and to further describe safety and tolerability.	Open-label, single dose	A single 27 mg dose of $^{(14)}C$ NGL via aqueous solution	6 healthy volunteers	Single dose	**PK**: PK parameters; accumulative radioactivity in urine and feces; metabolite profiling in plasma, urine and feces. **Safety**: AEs, vital signs, PE, laboratory assessments, 12-lead ECG and C-SSRS

Studies examining the effect of intrinsic factors						
Phase I **D3820C00020** Japanese single ascending dose/multiple ascending dose/Food effect study	Assess safety, tolerability and PK of NGL following single and multiple doses of NGL in healthy non-elderly and elderly Japanese volunteers under fasting and fed conditions	2 part study with 6 cohorts. Part 1: Double-blind, randomized, placebo-controlled, single and multiple dose study of 5 cohorts (4 non-elderly and 1 elderly healthy volunteers). Part 2: Open-label, randomized, 2-treatment, crossover study to investigate food-effect in non-elderly healthy volunteers.	Part 1: Non-elderly cohorts: 12.5 mg, 25 mg, 50 mg, and 100 mg NGL or NGL placebo via film-coated tablet, as single dose on day 1 and on days 3-10. Elderly cohort: 25 mg NGL film-coated tablet single dose Part 2: 25mg NGL film-coated table under fasted and fed conditions	Part 1: 40 adult healthy volunteers Part 2: 10 non-elderly health volunteer.	Part 1: A single dose for 1 day, with a 1-day washout, followed by 7 consecutive days. Part 2: 2 single 25 mg NGL doses, separated by a ≥7 day washout period	**Safety**: AEs, vital signs, physical examination, clinical chemistry and hematology; ECG and C-SSRS **PK**: Cmax, tmax, t½, $AUC_{(0-t)}$, AUC, Ae, Ae%, CLR, CL/F and Vz/F

Study Phase and Identifier	**Objectives**	**Design & type of control**	**Test products, Dosage regimen**	**No. of subjects rand/treated/ diagnosis of patients**	**Duration of treatment**	**Assessments**
Phase I **D3820C00009** Renal impairment study	Compare the PK of NGL and assess the safety & tolerability following a single 25 mg NGL dose in subjects with moderate or severe renal impairment or end stage renal disease (ESRD) and healthy volunteers with normal renal function	Open-label, non-randomized, single-dose, parallel-group study	25 mg NGL film-coated table. A single dose in subjects with normal, moderate, or severe renal function. Two doses in subjects with ESRD (1-2 hours after and 2 hours before hemodialysis), with a ≥7 day washout period.	32 (8 in each group)	1 day in the normal, moderate, or severe renal function groups, 2 days, separated by a washout period of ≥7 days, in the ESRD group.	**PK**: The primary variables were NGL AUC and C_{max} Secondary variables were NGL $AUC_{(0-t)}$, $AUC_{(0-24)}$, CL/F, V_z/F, t_{max}, and $t_{1/2}$; urine NGL A_e, f_e, and CL_R; and dialysate f_D and CL_D **Safety**: AEs, vital signs, physical examination, clinical laboratory measures, ECG and C-SSRS
Phase I **D3820C00010** Hepatic impairment study	Assess the PK and safety & tolerability of a single oral dose of 25 mg NGL in subjects with impaired hepatic function and in HVs with normal hepatic function and healthy volunteers with normal renal function	Open-label, nonrandomized, single dose, parallel group study	25 mg NGL, single dose	24 (8 subjects in each group)	Single dose	**PK**: Primary variables: C_{max} and AUC. Secondary variables: t_{max}, $t_{1/2}$, λ_z, $AUC_{(0-t)}$, $AUC_{(0-24)}$, CL/F, and V_z/F **Safety**: AEs, vital signs, physical examination, clinical laboratory measures, ECG, and CSSRS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

APPEARS THIS WAY ON ORIGINAL

Studies examining the effect of extrinsic factors

Phase I **D3820C00011** P-gp inhibitor (quinidine) drug interaction study	Part 1: Investigate the effect of quinidine on the PK of NGL in healthy volunteers Part 2: Investigate the effect of coadministration of NGL and quinidine on morphine-induced miosis Investigate the safety & tolerability of NGL when administered alone and in combination with morphine and/or quinidine.	Double-blind (for quinidine), randomized, 2-treatment, crossover, study. Part 1 & Part 2: 2-treatment crossovers with a ≥7-day washout period between treatments and between parts.	Part 1: 25 mg NGL film-coated tablet ± 600 mg quinidine Part 2: 25 mg NGL + intravenous morphine (5 mg/70 kg) + 600 mg quinidine.	Part 1: 38 healthy volunteers Part 2: 19 healthy volunteers	Part 1: 2 single doses of NGL separated by a ≥7-day washout period A ≥7-day washout period separating the 2 parts Part B: 2 single doses of NGL separated by a single dose with ≥7-day washout period	**PK**. Part 1: NGL C_{max}, t_{max}, $t_{1/2\lambda z}$, λ_z, AUC, $AUC_{(0-t)}$, $AUC_{(0-24)}$, CL/F, V_z/F Part 2: NGL, morphine, morphine-3-glucuronide, and morphine-6-glucuronide AUC, $AUC_{(0-24)}$, C_{max}, and tmax. Part 2: Change from baseline in morphine-induced miosis **Safety**: AEs, vital signs, Physical examination, clinical laboratory tests, ECG, telemetry and C-SSRS,

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Study Phase and Identifier	Objectives	Design & type of control	Test products, Dosage regimen	No. of subjects rand/treated/ diagnosis of patients	Duration of treatment	Assessments
Phase I **D3820C00012** Strong CYP3A inhibitor (ketonconazole) drug interaction study	Investigate the effect of ketoconazole on the PK of NGL in healthy volunteers, assess the safety and tolerability of NGL when administered alone and in combination with ketoconazole	Open-label, non-randomised, 3-treatment, cross-over	A single dose of 25 mg NGL film-coated tablet on Day 1, ketoconazole 400 mg once daily on Days 4-8, and a single dose of 25 mg NGL film-coated tablet with ketoconazole 400 mg on Day 7	22 healthy volunteers	2 single doses of NGL separated by a 5-day washout period	**PK**: C_{max}, t_{max}, $AUC_{(0-t)}$, $AUC_{(0-24)}$, AUC, λ_z, $t_{1/2,\lambda z}$, CL/F, V_z/F **Safety** AEs, vital signs, physical examination, clinical laboratory tests, ECG, telemetry and C-SSRS,
Phase I **D3820C00015** Strong CYP3A inducer (rifampin) drug interaction study	Investigate the effect of rifampin on the PK of NGL in healthy subjects, assess the safety and tolerability of NGL when administered alone and in combination with rifampin	Open-label, non-randomized, 3-treatment, cross-over	25 mg NGL film-coated tablet on Day 1, a 600 mg dose of rifampin once daily on Day 4 to Day 12, and a 25 mg NGL film coated tablet plus 600 mg rifampin on Day 13.	22 healthy volunteers	2 single doses of NGL separated by a an 11-day washout period	**PK**: C_{max}, t_{max}, AUC, $AUC_{(0-t)}$, $AUC_{(0-8)}$, $t_{1/2\lambda z}$, λ_z, $AUC_{(0-24)}$, CL/F, V_z/F **Safety** AEs, vital signs, physical examination, clinical laboratory tests, ECG, telemetry and C-SSRS
Phase I **D3820C00032** Moderate CYP3A inhibitor (diltiazem) drug interaction study	Investigate the effect of co-administration of diltiazem on the PK of NGL in healthy volunteers and assess the safety and tolerability of NGL when administered alone and in combination with diltiazem extended-release tablets	Open-label, non-randomized, cross-over	A 25 mg NGL film-coated tablet on Day 1, once-daily doses of 240-mg diltiazem XR on Days 4 through Day 6, a 25 mg NGL film-coated tablet plus 240-mg diltiazem on Day 7, and 240-mg diltiazem XR on Day 8.	43 Healthy volunteers	2 single doses of NGL separated by a 5-day washout period	**PK**: Primary variables: C_{max} and AUC Secondary variables: t_{max}, $t_{1/2\lambda z}$, λ_z, $AUC_{(0-t)}$, $AUC_{(0-24)}$, CL/F, and V_z/F **Safety**: AEs, vital signs, physical examination, clinical laboratory tests, ECG, telemetry and C-SSRS

APPEARS THIS WAY ON ORIGINAL

Table 3 Human pharmacodynamic studies completed with naloxegol

Study Phase and Identifier	Objectives	Design & type of control	Test products, Dosage regimen, Route of administration	No. of subjects rand/treated/ diagnosis of patients	Duration of treatment	Assessments
Phase 1 **D3820C00014** Thorough QTc study	Evaluate the effect of a single oral dose of NGL 25 mg and 150 mg on the changes in time-matched QTcF intervals versus placebo; with a single dose of moxifloxacin 400 mg as positive control	Double-blind, randomized, placebo-controlled, four-treatment crossover, with an open-label positive-control	25 mg NGL film-coated tablet 6 x 25 mg (150 mg) NGL film-coated tablet 400 mg Moxifloxacin NGL Placebo	52 healthy volunteers (48-51 per treatment)	Single 25 mg and 125 mg NGL doses, single 400 mg moxifloxacin dose, and placebo, given in a randomised order with ≥5 days washout period between treatments	**PD**: the changes in time-matched QTcF intervals compared with placebo **Safety**: AEs, vital signs, physical examination, telemetry, clinical chemistry and hematology, clinical assessment and C-SSRS **PK**: C_{max}, t_{max}, and $AUC_{(0-t)}$

Study ID and Location	Objective	Study Design and Type of Control	Test Product(s); system used	Type of Design
Section 4.2.2.4 Metabolism				
Sp-d3820-spe-0530			25 mg [^{14}C]NKTR-118	In vivo Mass Balance Study in Humans
LS-2008-607	Identify human specific metabolites; M:P ratios in plasma	Cross species Metabolic Profile Comparison NKTR-118		Metabolite profiling in plasma from clinical study 07-IN-NX002
RD00001768-00	Identify and semi-quantify metabolites	Cross species Metabolic Profile Comparison NKTR-118		Metabolite profiling in human urine from clinical study 07-IN-NX002
LS-2008-606	Identify human specific metabolites; M:P ratios in urine	Cross species Metabolic Profile Comparison NKTR-118 in urine		Metabolite profiling in human urine from clinical study 07-IN-NX002
Sp-d3820-spe-0535 MIST		Cross species metabolites comparison in plasma: human, rat, and dog		Metabolite profiling in human plasma from clinical study D3820C00020

Study Phase and Identifier	Objectives	Design & type of control	Test products, Dosage regimen, Route of administration	No. of subjects rand/treated/ diagnosis of patients	Duration of treatment	Assessments
Phase IIb **07-IN-NX003**	Evaluate efficacy of NGL at various doses Evaluate safety & tolerability of NGL, and identify an effective dose that preserves opioid-conferred analgesia Delineate dose-response for NGL across a range of underlying opioid doses Characterize the PK of NGL in patients	Double-blind, randomized, pbo-controlled, multiple-dose, dose-escalation	Pbo or NGL in aqueous solution 5, 25 or 50 mg QD. A 100 mg once daily dose was planned but cancelled due to the incidence of of GI DAEs in patients treated with the 50 mg dose (11/35 patients).	Cohort 1 (5 mg) Pbo: N=32, 27 completed NGL: N=33, 28 completed Cohort 2 (25 mg) Pbo: N=27, 27 completed NGL: N=30, 28 completed Cohort 3 (50 mg) Pbo: N=37, 31 completed NGL: N=35, 21 completed	4 weeks	**Efficacy**: Primary variable: change from baseline in SBM/week during the first week of double-blind treatment. Secondary variables: change from baseline in SBM/week for Weeks 2, 3, & 4 and averaged across the 4-week treatment, time to first laxation, patient assessments of constipation symptoms & quality of life, and rescue medication (bisacodyl) use. **Safety**: COWS, daily opioid requirements, NRS, AEs, DAEs, SAEs, laboratory assessments, ECG, VS, PE

In vitro studies:

Study ID and Location	Objective	Study Design and Type of Control	Test Product(s); system used	Type of Design
Section 4.2.2.4 Metabolism				
Section 4.2.2.6 Pharmacokinetic Drug Interactions				
LS-2007-064		Potential of Drug to inhibit CYP450 isoforms	CYP	Inhibition
ADME-AZS-Wave3-130226		Time-dependent inhibition on CYP	CYP	inhibition
LS-2007-073		Potential of Drug to induce CYP450 isoforms	CYP	induction
00003CYP_IND_HHEP		Potential of Drug to induce 1a2, 2b6, 3a4	CYP	Induction, Human hepatocytes
LS-2007-063		Metabolism of Drug by CYP	CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP2C8	Metabolism by Six CYP450 Isoforms; nonGLP
NKTR 118DMX3	Identify CYP450 and FMO enzymes responsible for NKTR-118 metabolism	Metabolism of Drug by CYP and FMO.	CYP	Metabolism in human liver microsomes
OPT-2010-113		Substrate of	Transporter	

		transporters		
OPT-2010-114		Inhibit transporters	Transporters	
Section 4.2.2.7 Others				
LS-2009-604		Determine Log(P) Pka values of NKTR-118		
RD00001548-00		Stability of NKT-10018 thawed fresh-frozen human plasma		
Section 4.2.2.2 Absorption				
RD00001771.00		In vitro permeability		Bi-directional permeability assay in Caco-2 cells, derived from human adenocarcinoma cell line
Section 4.2.2.3 Distribution				
LS-2007-024		Protein binding		Human, rat, mouse, dog, monkey

Table 4 Phase II and III efficacy and safety studies completed with naloxegol

Study Phase and Identifier	Objectives	Design & type of control	Test products, Dosage regimen, Route of administration	No. of subjects rand/treated/ diagnosis of patients	Duration of treatment	Assessments
Phase III **D3820C00004**	Compare response to NGL 12.5 and 25 mg doses with pbo in the treatment of patients with OIC Assess the safety and tolerability of NGL 12.5 and 25 mg	Multi-center, double-blind, randomized, pbo-controlled, parallel group. Randomization schedule was designed to ensure a minimum of 50% patients were LIR to allow evaluation of NGL in this subpopulation.	Patients received oral treatment of NGL 12.5 mg, or 25 mg, or pbo, once daily, as 2 tablets.	652/649: adult non-cancer pain patients on a stable maintenance opioid for a min of 4 weeks, who report a history of <3 SBMs/week and ≥ 1 OIC symptom at screening and have a confirmed diagnosis of OIC	12 week treatment period, preceded by an initial screening period up to 2 weeks, and a 2-week OIC confirmation period, and a 2-week FU visit.	**Efficacy: primary**: response to study drug during W 1 to 12 **Key secondary end-points**: response to study drug in the LIR subgroup during W 1 to 12, time to first post-dose laxation, and mean number of days per week with ≥ 1 SBM Other secondary end-points: change in OIC symptoms (straining, stool consistency, and percent days/week with complete evacuation, PAC-SYM, and PAC-QoL). **Safety**: adverse events (AEs), treatment-related AEs, SAEs, DAEs, AEOSIs, mean daily opioid dose , NRS pain score, mHS, laboratory assessments, VSs, ECG, PE, C-SSRS, overdose. For variables, see the individual CSRs.
Phase III **D3820C00005**	Compare response to NGL 12.5 and 25 mg doses	Multi-center, double-blind, randomized, pbo-	Patients received oral treatment of NGL 12.5 mg,	700/697 non-cancer pain patients on a stable	12 week treatment period, preceded by	**Efficacy: primary**: response to study drug during W 1 to 12 **Key secondary end-points**: response to study drug in the

Study Phase and Identifier	Objectives	Design & type of control	Test products, Dosage regimen, Route of administration	No. of subjects rand/treated/ diagnosis of patients	Duration of treatment	Assessments
	with pbo in the treatment of patients with OIC Assess the safety and tolerability of NGL 12.5 and 25 mg	controlled, parallel group. Randomization schedule was designed to ensure a minimum of 50% patients were LIR to allow evaluation of NGL in this subpopulation.	or 25 mg, or pbo, once daily, as 2 tablets.	maintenance opioid for a min of 4 weeks, who report a history of <3 SBMs/week and ≥ 1 OIC symptom at screening and have a confirmed diagnosis of OIC	an initial screening period up to 2 weeks, as well as a 2-week OIC confirmation period, and a 2-week FU visit.	LIR subgroup during W 1 to 12, time to first post-dose laxation, and mean number of days per week with ≥ 1 SBM Other secondary end-points: change in OIC symptoms (straining, stool consistency, and percent days/week with complete evacuation, PAC-SYM, and PAC-QoL. **Safety**: adverse events (AEs), treatment-related AEs, SAEs, DAEs, AEOSIs, mean daily opioid dose , NRS pain score, mHS, laboratory assessments, VSs, ECG, PE, C-SSRS, overdose. For variables, see the individual CSRs.
Phase III **D3820C00006**	Part A. Compare response to NGL 12.5 and 25 mg doses with pbo in the treatment of patients with cancer-related pain and OIC Assess the	Part A: double-blind, randomized, pbo-controlled, parallel group study Part B: active treatment extension. .	Part A: Patients received oral treatment of NGL 12.5 mg, or 25 mg, or pbo, once daily, as 2 tablets. Part B: Patients who were on	Part A: 14/14 Part B: 9/9 Adult patients with a histologically or cytologically confirmed neoplasm and with a life expectancy of ≥3 months who were receiving a stable	Part A: 4-week double-blind treatment period, preceded by an initial screening period (14 days), and a 2-week OIC	**Efficacy**: **primary**: response to study drug during W 1 to 4 **Secondary efficacy**: Part A and Part B: change from baseline in RFBMs/week, mean number of days per week with ≥ 1 RFBM, and change from baseline in PAC-SYM and PAC-QOL total scores and domain scores. Part A only: time to first post-dose RFBM, straining stool consistency (BSS), percent

Study Phase and Identifier	Objectives	Design & type of control	Test products, Dosage regimen, Route of administration	No. of subjects rand/treated/ diagnosis of patients	Duration of treatment	Assessments
	safety and tolerability of NGL 12.5 and 25 mg Part B: Assess the safety and tolerability of NGL 12.5 and 25 mg during an additional 12 weeks of treatment..		active treatment were to be allocated to the same NGL treatment/dose and patients who were on pbo were to be allocated to receive NGL 25 mg.	maintenance opioid regimen for a min of 4 w prior to screening. who report a history of <3 rescue-free bowel movements (RFBMs)/week and ≥ 1 OIC symptom at screening and have a confirmed diagnosis of OIC	confirmation period. Patients who discontinue study treatment in Part A or who choose not to continue into Part B will have a 2-week FU visit and a FU telephone call 18 weeks after randomisation . Part B: 12-week treatment period, and a 2-week FU visit	days/week with complete evacuation. Part B only: duration of response during the 12-week extension period. **Safety**: adverse events (AEs), treatment-related AEs, SAEs, DAEs, AEOSIs, mean daily opioid dose , NRS pain score, mHS, laboratory assessments, VSs, ECG, PE, C-SSRS. For variables, see the individual CSRs.
Phase III **D3820C00007**	Compare NGL 12.5 and 25 mg with pbo regarding long-term safety and tolerability in the treatment of OIC using	12-week extension of the Phase III, multicenter, double-blind, randomized, pbo-controlled, parallel group	NGL 12.5 or 25 mg tablets, or matching pbo, oral, QD.	302 rollover/297 treated. Patients who successfully completed Study D3820C00004 and continued to receive a stable opioid regimen.	12 weeks	**Safety** AEs, treatment-related AEs, SAEs, DAEs, AEOSIs, mean daily opioid dose, NRS pain score, mHS, laboratory assessments, VSs, ECG, PE, C-SSRS, overdose. **Efficacy**: PAC-SYM, PAC-QOL, mean rescue medication (bisacodyl) dose

Study Phase and Identifier	Objectives	Design & type of control	Test products, Dosage regimen, Route of administration	No. of subjects rand/treated/ diagnosis of patients	Duration of treatment	Assessments
	descriptive statistics Assess the impact of NGL 12.5 and 25 mg on symptoms of constipation and quality of life	12 week study D3820C00004. Patients continued on the same randomized treatment taken in the preceding study.				
Phase III **D3820C00008**	Assess long-term safety and tolerability of NGL 25 mg; evaluate the long-term safety and tolerability of NGL 25 mg compared with Usual Care using descriptive statistics.	52-week, multi-center, open-label, randomized, parallel group, safety and tolerability study versus Usual Care. Patients could be either rollover patients from Study D3820C00005 or Study D3820C00007, or new to the NGL program.	NGL 25 mg tablets, oral, QD. Patients assigned to Usual Care followed a laxative treatment regimen for OIC determined by the investigator according to his/her best clinical judgment, excluding peripheral μ-opioid antagonists.	844 patients randomized (760 new and 84 rollover), 840* treated. Non-cancer pain patients on a stable maintenance opioid regimen. New patients: stable opioid regimen for ≥4 weeks, with a history of <3 SBMs/week and ≥1 OIC symptom at screening and a confirmed diagnosis of OIC	52 weeks	**Safety** AEs, treatment-related AEs, SAEs, DAEs, AEOSIs, mean daily opioid dose, NRS pain score, mHS, laboratory assessments, VS, ECG, PE, C-SSRS, overdose. **Efficacy:** mean rescue medication (bisacodyl) dose

Table 1 Clinical biopharmaceutic studies completed with naloxegol

Study Phase and Identifier	Objectives	Design & type of control	Test products, dosage regimen,	N and type of subjects rand/treated	Duration of treatment	Assessments
Phase I **08-PNL-04** Bioavailability study	Evaluate the bioavailability of 100 mg NGL tablet relative to 100 mg NGL solution	Open-label, randomized, single-dose, active-controlled 2-treatment, crossover	Single doses of 100 mg NGL solution 100 mg NGL film-coated tablet	20 healthy volunteers	Single-dose treatment days, separated by ≥8-day washout period	**PK**: C_{max}, t_{max}, $AUC_{(0-t)}$, $AUC_{(0-inf)}$, $AUC_{(0-24)}$, $t_{1/2}$ **Safety**: AEs, BP, pulse rate, respiratory rate, temperature, physical examination, ECG, hematology, clinical chemistry, urinalysis
Phase I **D3820C00025** Bioavailability and food effect study	Assess relative bioavailability of 1) fast and slow dissolution NGL oxalate formulations compared to the Ph III NGL formulation 2) fast dissolution formulation and Ph III formulation under fasted and fed conditions	Open-label, randomized, single-dose, active-controlled, 2-part design. Part A: 3-treatment crossover Part B: 2-treatment crossover	Part A: 25 mg NGL oxalate slow dissolution tablet, 25 mg NGL oxalate fast dissolution tablet, 25 mg NGL film-coated tablet, under fasted conditions. Part B: 25 mg NGL oxalate fast dissolution tablet, 25 mg NGL film-coated tablet, under fed conditions.	24 healthy volunteers	5 single-dose treatment days, separated by ≥7-day washout periods	**PK**: C_{max}, t_{max}, λz, $t_{1/2\lambda z}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, $AUC_{(0-inf)}$, CL/F, and Vz/F **Safety**: AEs, vital signs, physical examination, 12-lead ECG, clinical laboratory assessments, C-SSRS
Phase I **D3820C00018** Pivotal bioequivalence	Demonstrate bioequivalence between the Ph III NGL formulation and the NGL oxalate commercial formulation under fasted conditions, Assess the effect of food on the PK of the naoxegol commercial formulation	Open-label, randomised, single dose, active controlled, 3-treatment crossover	25 mg NGL film-coated tablet (Phase III formulation), under fasted conditions 25 mg NGL oxalate film-coated tablet (intended commercial formulation), under fasted and fed conditions	42 adult healthy volunteers	3 single-dose treatment days, separated by ≥7-day washout periods	**PK primary**: C_{max}, AUC, t_{max}, $t_{1/2\lambda z}$, λ_z, $AUC_{(0-t)}$, $AUC_{(0-24)}$, CL/F, and V_z/F **PK food effect**: C_{max}, AUC, t_{max}, $t_{1/2\lambda z}$, λ_z, $AUC_{(0-t)}$, $AUC_{(0-24)}$, CL/F, and V_z/F **Safety**: AEs, vital signs, PE, 12-lead ECG, clinical laboratory assessments, C-SSRS

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDHYA K APPARAJU
10/30/2013

ELIZABETH Y SHANG
10/30/2013

SUE CHIH H LEE
10/30/2013