CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204760Orig1s000

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Serial Number:	204760
Drug Name:	Movantik (Naloxegol Oxalate) tablets
Indication(s):	Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain
Applicant:	AstraZeneca Phamaceuticals LP
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Biometrics Division:	Division of Biometrics 3 (DB3)
Statistical Reviewer:	Wen-Jen Chen, Ph.D.
Concurring Reviewer:	Mike Welch, Ph.D.
Medical Division:	Gastroenterology and Inborn Error Products (DGIEP)
Clinical Team:	Aisha Peterson-Johnson, M.D., Anil Rajpal, M.D. (TL)
Project Manager:	Maureen Dewey
Statistical Keywords:	Clinical studies; NDA review.

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

Based upon this reviewer's efficacy comparisons on the primary endpoint and the applicant's analysis results on the primary endpoint and the key secondary endpoints, data submitted by the applicant support the efficacy of Movantik 25 mg.

1.2 Brief Overview of Clinical Study

Studies D3820C00004 and D3820C00005 were Phase 3, multi-center, double-blind, randomized, placebo-controlled, parallel group studies. The primary objective for both studies was to compare the efficacy of Movantik (NKTR-118) 12.5 mg and 25 mg with placebo in the treatment of patients who have opioid-induced constipation (OIC). Study duration was up to 18 weeks, consisting of an initial screening period lasting up to 2 weeks, a 2-week OIC confirmation period, a 12-week treatment period, and a follow-up visit 2 weeks after the last dose of study drug. In addition, a total of 652 patients in Study D3820C00004 and 700 patients in Study D3820C00005 were randomized in a 1:1:1 ratio to receive 12.5 mg or 25 mg of Movantik or placebo once daily for 12 weeks.

The primary efficacy endpoint for both studies was response (responder/non-responder) to study drug during Weeks 1 to 12. 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 of 12 weeks, and at least 3 out of the last 4 weeks.

1.3 Statistical Issues and Findings

The comments given below pertain to Movantik 25 mg and are based upon the applicant's analysis results in the NDA submission and the applicant's response document to the Agency IR letter. Since Movantik 12.5 mg was not shown to be superior to placebo in one study, substantial evidence of efficacy for that dose was not demonstrated.

Comments on Primary endpoint

Study D3820C00004

- The response rate assessed by the primary endpoint in Movantik 25 mg group was significantly higher than that of placebo (44.4% vs. 29.4%) using the applicant's ITT population.

- Based upon the applicant's response to the IR and the re-analysis based on the reviewer's All Randomized and FAS populations conducted by the applicant, the response rate of Movantik 25 mg remained significantly higher than that of placebo.

- No center was deemed to have an abnormally large rate difference to dominate the superiority of Movantik 25 mg versus placebo.

- Therefore, it is the reviewer's conclusion that for Study D3820C00004, the superiority of Movantik 25 mg to placebo assessed by the primary endpoint is supported by the submitted data**.**

Study D3820C00005

- The response rate assessed by the primary endpoint in the Movantik 25 mg was significantly higher than that of placebo (39.7% vs 29.3%) using the applicant's ITT population.

- Based upon the applicant's response to the IR and the re-analysis based on the reviewer's All Randomized and FAS populations, the response rate of Movantik 25 mg remained significantly higher than that of placebo.

- The sizes of response rate differences of Movantik 25 mg versus placebo were evenly distributed across centers, and no center was deemed to have abnormal large rate difference to dominate the superiority of Movantik 25 mg versus placebo.

- Therefore, it is the reviewer's conclusion that for Study D3820C00005, the superiority of Movantik 25 mg to placebo assessed by the primary endpoint is supported by the submitted data**.**

Comments on Key Secondary endpoints – Studies D3820C00004 and D3820C00005

- Based on the original NDA submission, the applicant's efficacy comparisons of Movantik 25 mg versus placebo show positive results in favor of Movantik for the following three key secondary endpoints:
  Response to study drug in the LIR subgroup during Weeks 1 to 12;
  Time to first post-dose laxation without use of rescue laxatives within 24 hours;
  Mean number of days per week with at least one SBM during Weeks 1 to 12.

- Based upon the applicant's response document dated 01/10/2014, the efficacy comparisons of Movantik 25 mg versus placebo assessed for the three key secondary endpoints using the All Randomized population also showed positive results in favor of Movantik.

2.0 INTRODUCTION

2.1 Overview

In the cover letter, the applicant made the following foreword with regard to Movantik

(Naloxegol):

> Naloxegol functions as a peripherally-acting mu-opioid receptor antagonist (PAMORA) in the gastrointestinal tract, thereby decreasing the constipating effects of opioids without impacting opioid-mediated analgesic effects on the central nervous system. PAMORAs are a new and evolving class of drugs. Although drugs within the PAMORA class may share a similar mechanism of action, they have distinct pharmacological differences providing a distinct product profile.

For this NDA submission, the applicant conducted two phase 3 trials (Studies D3820C00004 and D3820C00005) to support the use of Movantik for treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

Study D3820C00004

The primary objective of this Phase 3, multi-center, double-blind, randomized, placebo-controlled, parallel group study was to compare the efficacy of Movantik (NKTR-118) 12.5 mg and 25 mg with placebo in the treatment of patients who have OIC. This study was conducted in the U.S., Australia, Germany, and Slovakia. The study duration was up to 18 weeks, consisting of an initial screening period lasting up to 2 weeks, a 2-week OIC confirmation period, a 12-week treatment period, and a follow-up visit 2 weeks after the last dose of study drug. A total of 641 patients randomized across 98 centers were included in the intent- to-treat (ITT) population.

The primary efficacy endpoint is response (responder/non-responder) to study drug Movantik during Weeks 1 to 12. A responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 9 out of 12 weeks, and at least 3 out of the last 4 weeks.

Three key secondary endpoints are presented below:

1. Response rate during Weeks 1 to 12 in the LIR subgroup.
2. Time (in hours) to first post-dose laxation without the use of rescue laxatives.
3. Mean number of days per week with at least one SBM during the entire 12 weeks of treatment.

Study D3820C00005

The primary objective and the study design for the Study D3820C00005 was the same as that for Study D3820C00004. Study D3820C00005 was conducted in the U.S., Belgium, Croatia, Czech Republic, Hungary, Spain, Sweden, and the United Kingdom. A total of 696 patients randomized across 117 centers were included in ITT population.

During the course of the review, several deficiencies were noted, common to both studies (D3820C00004 and D3820C00005). The Agency issued an Information Request dated 12/20/2013 to have the applicant address the following concerns:

- Several subjects randomized in the phase 3 studies had been previously randomized in the clinical development program at different centers and were not included in the ITT or mITT populations. In order to show that these subjects did not adversely affect the efficacy analysis results, the applicant was requested to perform primary analysis for the primary and key secondary endpoints using a FAS (defined by the reviewer as all randomized patients who received at least one dose of study drug including those randomized more than once) and the All-Randomized population (defined by the reviewer as all randomized patients including those randomized more than once).
- In order to validate the mixed model for repeated measures results for the key secondary endpoint defined as mean number of days per week with at least one SBM during the entire 12 weeks of treatment, the applicant was requested to perform a blocked two-sample Wilcoxon rank sum (WRS) test stratified by pooled centers.
- Re the applicants missing data handling strategy, the SAP indicated that if fewer than four days of data are recorded within a particular week, the data for that week would be considered insufficient and the rate would be set to missing. The applicant was requested to clarify, for the primary analysis, if the missing rate for that week was to be analyzed as a non-response (treatment failure).

The applicant's response document was received by the Agency on 01/10/2014 and the applicant's responses are discussed in Sections 3.1.1 and 3.1.2.

2.2 Data Sources

To assess the clinical efficacy of Studies D3820C00004 and D3820C00005 used in support of the proposed indication, this reviewer reviewed the original electronic NDA supplement submission, dated 09/16/2013 and the response documents (dated 01/10/2014) to the Agency IR letter (dated 12/20/2013), located at "\\CDSESUB1\EVSPROD\NDA204760\204760.enx".

3.0 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

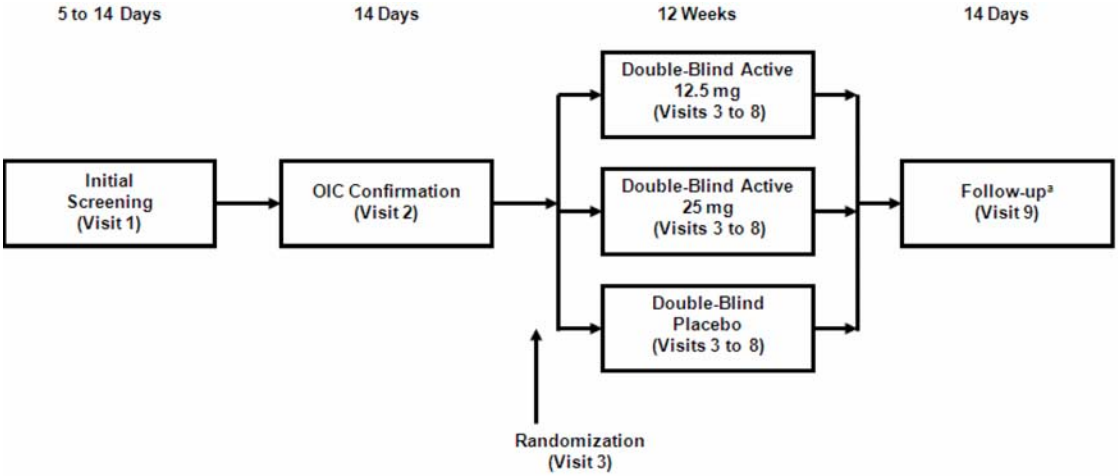
3.1.1 Study D3820C00004

3.1.1.1 Design and Endpoints

The primary objective of this Phase 3, multi-center, double-blind, randomized, placebo-controlled, parallel group study was to compare the efficacy of Movantik (NKTR-118) 12.5 mg and 25 mg with placebo in the treatment of patients who have OIC. This study was conducted in the U.S., Australia, Germany, and Slovakia. The study duration was up to 18 weeks, consisting of an initial screening period lasting up to 2 weeks, a 2-week OIC confirmation period, a 12-week treatment period, and a follow-up visit 2 weeks after the last dose of study drug.

Patients who successfully completed the 12-week treatment period were eligible to participate in a separate safety extension study. However, while the study was still ongoing, the safety extension study was closed for enrollment because it had met its recruitment goals (enrolled a sufficient number of patients for the long-term safety analyses). Figure 3.1.1.1.1 shows the design of the study and the sequence of treatment periods.

Figure 3.1.1.1.1 (Applicant's) Flow chart of study design - Study D3820C00004



[a] Patients who participated in the extension study were not required to complete the Follow-up visit
Source: Figure 1 at page 19 in Study D3820C00004 Report.

Approximately 1300 patients were to be screened to obtain 630 randomized patients at approximately 120 centers. At screening, patients received an electronic diary (eDiary) device and training on how to record information using the device. Patients were requested to use the eDiary to record the following information: date and time of BMs (recorded at the time of each BM), stool consistency (Bristol Stool Scale, BSS) (recorded at the time of each BM), straining (recorded at the time of each BM), complete/incomplete evacuation (recorded at the time of each BM), pain level (Numeric Rating Scale, NRS) recorded each evening, date and time of use of laxative rescue medication (bisacodyl or enema) recorded at the time that medication was taken, and date and time of use of opioid medication for breakthrough pain recorded at the time that medication was taken as well as the medication and dose administered. Patients completed the eDiary daily through the end of randomized treatment.

A spontaneous bowel movement (SBM) was defined as a BM without the use of rescue laxatives (bisacodyl or enema) administered in the previous 24 hours. Once patients had met initial screening requirements and had completed at least 5 days of recording using the eDiary device, they returned for Visit 2. Bisacodyl for use as a rescue medication was dispensed to patients at Visit 2, and at each visit thereafter until Visit 8. Confirmation of OIC was established between Visits 2 and 3.

Patients returned for Visit 3, 2 weeks after Visit 2. The eDiary was reviewed with patients. Patients who failed OIC or stable opioid dose confirmation or who discontinued due to inability

to use the recording device correctly returned the device and were not randomized. Patients with confirmed OIC and who had continued on a stable maintenance opioid regimen were randomized. Patients were disqualified from randomization if they consumed greater than four opioid doses for breakthrough pain per day for more than 3 days during the 2-week OIC confirmation period, or if their maintenance opioid dosing regimen was modified during this same period.

Randomization occurred at the onset of the 12-week, double-blind treatment period at Visit 3. Patients were stratified based on their response to three levels of laxative use: (laxative inadequate responder (LIR), laxative adequate responder (LAR), and laxative unknown responder (LUR) and were randomly assigned in a 1:1:1 ratio (approximately 210 patients per treatment group) to receive placebo, or Movantik (NKTR-118) at a dose of 12.5 or 25 mg once daily (QD), with a minimum of 50% of patients randomized in the LIR category. Patients were centrally randomized using the Interactive Voice Response System.

The double-blind treatment period consisted of Visits 3 (Day 1), 4 (Day 8), 5 (Day 15), 6 (Day 29), 7 (Day 57), and 8 (Day 85). During the double-blind treatment period, patients were required to continue daily eDiary recording. Patients were instructed that they were to complete the eDiary every day, including days they had study visits. Compliance with the eDiary was assessed remotely and patients were contacted if data were not being recorded. Patients were also asked to bring the eDiary recording device with them to each visit, during which their recordings and proper use of the device were reviewed.

Patients who did not enter the safety extension study were asked to participate in a follow-up visit (Visit 9, Day 99, 2 weeks after Visit 8). Following Visit 8, these patients could resume any constipation regimen that patients and the investigator felt appropriate.

The primary efficacy endpoint was defined as response (responder/non-responder) to study drug during Weeks 1 to 12, where a weekly responder was defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline. Response was defined as having a weekly response for at least 9 out of 12 weeks, and at least 3 out of the last 4 weeks.

Three key secondary efficacy endpoints, included in the multiplicity adjustment, supported the primary objective. These are listed below:

- Response (responder/non-responder) to study drug in the laxative inadequate response (LIR) subgroup during Weeks 1 to 12, where a responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 9 out of 12 weeks, and at least 3 out of the last 4 weeks.
- Time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours.
- Mean number of days per week with at least 1 SBM during Weeks 1 to 12.

Other secondary efficacy variables were deemed exploratory and not further discussed in this review:

- Response (responder/non-responder) to study drug during Weeks 1 to 4, where a responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 3 out of the first 4 weeks.
- Response (responder/non-responder) to study drug in the LIR subgroup during Weeks 1 to 4, where a responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 3 out of the first 4 weeks.
- Change from baseline in the SBMs/week for Weeks 1 to 4 and 1 to 12.
- Time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours in the LIR subgroup.
- Mean number of days per week with at least 1 SBM for Weeks 1 to 4.
- Change from baseline in the mean degree of straining for Weeks 1 to 4 and 1 to 12.
- Change from baseline in the mean stool consistency (BSS) for Weeks 1 to 4 and 1 to 12.
- Percentage of days with complete SBM (CSBM) for Weeks 1 to 4 and 1 to 12.

The intent-to-treat (ITT) analysis set included all randomized patients, with the exception of 11 patients who were found to have been randomized multiple times at different centers. The ITT analysis set was considered the primary analysis set and was used for all efficacy endpoints.

The modified intent-to-treat (mITT) analysis set (a subset of the ITT analysis set) consisted of all randomized patients (not including those randomized multiple times) who received at least one dose of study drug and had at least one post-baseline efficacy assessment. As a sensitivity analysis, the primary analysis was repeated in the mITT analysis set.

The All Randomized analysis set refers to the ITT plus the 11 subjects who were randomized more than once. In the Agency IR dated 12/20/2013, the applicant was requested to reanalyze the primary and key secondary endpoints using this population and a FAS population defined as all randomized subjects who received study drug.

The per-protocol (PP) analysis set included only those ITT patients who had no important protocol deviations. Analyses of the primary efficacy endpoint, responders over the entire 12-week period in the ITT analysis set, were repeated on the PP analysis set.

The Safety analysis set included all randomized patients who received at least one dose of study drug, with the exception of patients who were found to have randomized multiple times within the program at different centers. The Safety analysis set was used to assess safety and tolerability variables. Patients were analyzed according to the treatment they first received.

3.1.1.2 Statistical Methodologies

Cochran-Mantel-Haenszel (CMH) tests stratified by the response to laxatives at baseline (LIR, LAR, LUR) were applied to compare the treatment differences of NKTR-118 12.5 mg vs. placebo and NKTR-118 25 mg vs. placebo assessed by the response rate of Weeks 1 to 12 (primary endpoint) using ITT analysis set as the primary analysis. The primary efficacy analysis was repeated on the mITT and PP analysis sets as sensitivity analyses.

The following three key secondary efficacy comparisons included in the multiplicity framework were based on the ITT analysis set, their numbering below indicating the order in which the secondary variables were tested in the Multiple Testing Procedure (MTP) for each dose group.

1. Comparison of the response rate during Weeks 1 to 12 of NKTR-118 12.5 mg vs. placebo and NKTR-118 25 mg vs. placebo in the LIR subgroup. Difference between treatment groups in response rate were analyzed using Chi-square tests. The treatment effect was characterized by the relative risk (RR; NKTR-118/placebo) with associated 2-sided 95% CIs.

2. Comparison of time (in hours) to first post-dose laxation without the use of rescue laxatives. Treatment group differences for the time to first SBM were analyzed using log-rank tests stratified by the response to laxatives at baseline (LIR, LAR, LUR). The treatment effect was characterized by the hazard ratio (NKTR-118/placebo) for each dose group, with associated 95% CIs.

3. Comparison of the mean number of days per week with at least one SBM during the entire 12 weeks of treatment of NKTR-118 12.5 mg vs. placebo and NKTR-118 25 mg vs. placebo. Differences between treatment groups in the number of days per week with at least one SBM were analyzed using a mixed model for repeated measures (MMRM). Descriptive statistics for the mean number of days per week over Weeks 1 to 12 were presented by treatment group.

The applicant indicated that in order to control the overall type I error rate to be less than 0.05 for the multiple comparisons in the primary and the key secondary endpoints, a MTP with Bonferroni-Holm over groups, and fixed-sequence within groups was applied. Specifically, there were two group comparisons defined by the NKTR-118 doses of 12.5 mg versus placebo and 25 mg versus placebo. Within each group comparison, there was a pre-defined fixed-sequence MTP of comparisons of the primary and key secondary endpoints vs. placebo (i.e., 12-week responder analysis in LIR subgroup, time to first post-dose laxation without laxative use in the previous 24 hours, and mean number of days per week with at least one SBM over the 12 week treatment period) at level of $\alpha/2$. If the null hypotheses for one group comparison was rejected entirely (i.e., significant difference between active vs. placebo for all 4 endpoints at $\alpha = 0.025$), the level was increased to α (ie, 0.05) for the other group comparison. This amounted to using Bonferroni-Holm over groups, and fixed-sequence within groups. This multiplicity adjustment method followed the general results described by Bretz et al.[1] and Burman et al.[2]

For sample size determination, the applicant indicated that a sample size of 105 patients per group would have been needed to detect a difference of 25% in response rate (60% on NKTR-118 and 35% on placebo) with 90% power at two-sided alpha level of 0.025. However, in order to provide an adequate power to detect a treatment difference in LIR subgroup (assuming LIR is

1 Bretz F, Maurer W, Brannath W, Posch M, A graphical approach to sequentially rejective multiple test procedures, Statistics in Medicine, 2009; 28:586–604

2 Burman CF, Sonesson C, Guilbaud O, A recycling framework for the construction of Bonferroni-based multiple tests, Statistics in Medicine, 2009; 28:739–761.

50% of the total study population), it was recommended that 210 patients per group (total 630 patients for 3 treatment groups) be randomized to the study.

The assumptions on expected response rate were referenced from the NKTR-118 Phase II study and from other similar drugs based on response over 4 weeks. It was assumed that a similar magnitude in relative treatment effect would hold for the response assessed over 12 weeks.

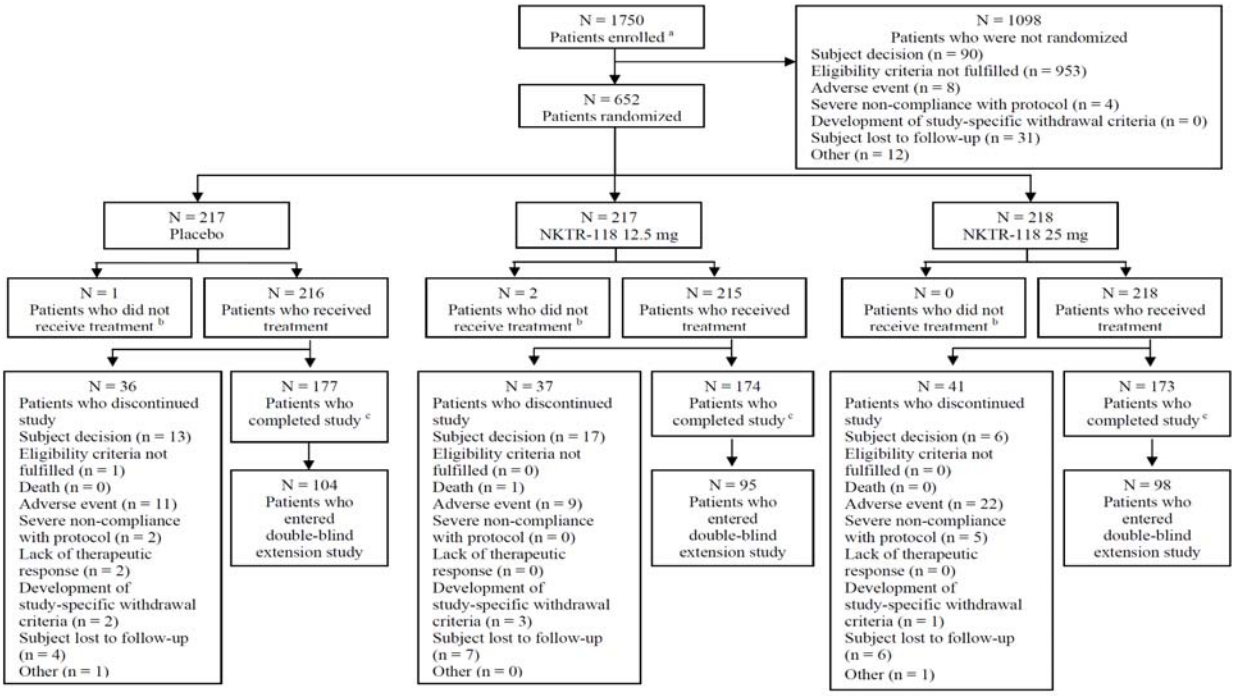
In the statistical analysis plan (SAP), the applicant indicated missing data entries in the eDiary would not be imputed. Using data from the eDiary, the SBMs/week will be calculated for each week as (total number of SBMs during the time period of interest/number of days) x 7 where the denominator is the number of days during the time period in which the patient records data. If fewer than 4 days of data are recorded within a particular week, the data for that week will be considered insufficient and the rate will be set to missing for that week.

In the Agency IR letter, the applicant was asked to clarify if the missing rate for that week was to be analyzed as a non-response (treatment failure). The applicant indicated that it would be analyzed as a non-response.

3.1.1.3 Patient Disposition

The first subject was enrolled on 3/14/2011 and the last subject completed the study on 8/16/2012. The disposition of the patients in this study (which consisted of up to a 2-week screening period, a 2-week OIC confirmation period, and a 12-week treatment period) is summarized in Figure 3.1.1.3.1 below.

Figure 3.1.1.3.1 (Applicant's) Patient disposition flow chart - Study D3820C00004



a After 22 March 2012, screening of non-LIR patients was stopped to ensure that a minimum of 50% of patients randomized would be LIR. Of the 652 patients randomized into the study, 553 patients were screened on or before 22 March 2012.
b Randomized patients did not receive treatment due to eligibility criteria not fulfilled (1 patient in the placebo group and 2 patients in the NKTR-118 12.5 mg group).
c A total of 11 patients who completed the study (4 patients each in the NKTR-118 25 mg and 12.5 mg groups and 3 patients in the placebo group) had been previously randomized within the NKTR-118 program at a different study center. These patients are included in the number of patients who received treatment but were excluded from the ITT and Safety analysis sets and are therefore not included as patients who completed the study.
ITT intent-to-treat; LIR Laxative Inadequate Responder/Response.
Source: Figure 2 at page 61 in Study D3820C00004 Report

A total of 1750 patients entered screening. A total of 652 patients completed the OIC confirmation period were randomized, and entered the double-blind treatment period. Of these patients, 649 (99.5%) received treatment, and 524 (80.4%) completed the study (defined as completing Visit 8 [Week 12] for patients who continued into the extension study, or completing Visit 9 [Week 14] for patients who did not continue into the extension study).

Patients who did not enter the extension study were to participate in a follow-up visit two weeks after the last dose of study drug. Overall, 297 patients from the ITT analysis set (45.6% of the total randomized) completed the study and continued into double-blind extension study D3820C00007.

A total of 11 additional patients (1.7%) completed the study, but had previously or concurrently participated in the NKTR-118 program at another study center (4 patients each in the NKTR-118 25 mg and 12.5 mg groups and 3 patients in the placebo group). These patients were identified prior to database lock and were not included in the ITT, or Safety analysis sets. The remaining

text in this section describes the patients in the ITT analysis set; however, percentages are based on the total number of patients randomized.

A total of 114 patients (17.5%) who received treatment discontinued the study. The most common reason for discontinuation from the study was AEs (42 patients; 6.4% overall). A greater proportion of patients were withdrawn due to AEs in the NKTR-118 25 mg group (22 patients; 10.1%) compared with the NKTR-118 12.5 mg group (9 patients; 4.1%) and the placebo group (11 patients, 5.1%). The second most common reason for discontinuation from the study was subject decision (36 patients; 5.5% overall). A smaller proportion of patients were withdrawn due to subject decision in the NKTR-118 25 mg group (6 patients; 2.8%) compared with the NKTR-118 12.5 mg group (17 patients; 7.8%) and the placebo group (13 patients, 6.0%).

A total of 641 patients from 98 centers across the following four countries were randomized and included in the ITT analysis: Slovakia (6 patients: 0.9%), Australia (1 patient: 0.2%), Germany (8 patients; 1.2%), and the US (637 patients; 99.4%).

The analysis sets and the number of patients in each analysis set are summarized in Table 3.1.1.3.1. The applicant indicated that all decisions on the inclusion or exclusion of patients from analyses were made while the data were still blinded. Additional analysis sets (not shown in the table) were defined by the reviewer in the Agency IR as the All Randomized population (all randomized including the 11 patients who were randomized multiple times) and the FAS population (all randomized who received study drug).

Table 3.1.1.3.1 (Applicant's) Summary of analysis sets - Study D3820C00004

	Number of patients			
	Placebo (N = 217)	**NKTR-118 12.5 mg (N = 217)**	**NKTR-118 25 mg (N = 218)**	**Total (N = 652)**
All randomized patients	217	217	218	652
Intent-to-treat analysis set	214	213	214	641
Patients excluded from intent-to-treat set	3	4	4	11
Modified Intent-to-treat analysis set	211	211	212	634
Patients excluded from modified intent-to-treat set	6	6	6	18
Patients included in per-protocol analysis set	199	201	201	601
Patients excluded from per-protocol analysis set	18	16	17	51
Patients included in safety analysis set	213	211	214	638
Patients excluded from safety analysis set	4	6	4	14

Note: For the safety analysis set data are summarized according to treatment first received. For all other analysis sets, data are summarized by randomized treatment.

Note: The ITT analysis set includes all randomized patients excluding patients who were randomized multiple times at different centers.

Note: The mITT analysis set includes all ITT patients who received at least 1 dose of IP (NKTR-118 or placebo) and had at least 1 post-baseline efficacy assessment.

Source: Table 8 at page 65 in Study D3820C00004 Report.

3.1.1.4 Demographics and Baseline Characteristics

The demographic and key baseline characteristics of study patients are summarized in Table 3.1.1.4.1

Table 3.1.1.4.1 (Applicant's) Demographic characteristics (Intent-to-treat analysis set)
- **Study D3820C00004**

Demographic characteristics	Placebo (N = 214)	NKTR-118 12.5 mg (N = 213)	NKTR-118 25 mg (N = 214)	Total (N = 641)
Age (years) [a]				
n	214	213	214	641
Mean	52.9	51.9	52.2	52.3
SD	9.99	10.43	10.29	10.23
Median	53.0	52.0	53.0	53.0
Min	20	19	18	18
Max	83	76	79	83
Age group (years), n (%)				
Age <50	71 (33.2)	81 (38.0)	73 (34.1)	225 (35.1)
≥50 to <65	121 (56.5)	113 (53.1)	121 (56.5)	355 (55.4)
≥65 to <75	17 (7.9)	17 (8.0)	17 (7.9)	51 (8.0)
≥75	5 (2.3)	2 (0.9)	3 (1.4)	10 (1.6)
Body mass index (BMI) (kg/m^2)				
<18.5	0	1 (0.5)	1 (0.5)	2 (0.3)
18.5-<30	108 (50.5)	98 (46.0)	102 (47.7)	308 (48.0)
≥30	106 (49.5)	114 (53.5)	111 (51.9)	331 (51.6)
Sex, n (%)				
Male	74 (34.6)	78 (36.6)	96 (44.9)	248 (38.7)
Female	140 (65.4)	135 (63.4)	118 (55.1)	393 (61.3)
Race, n (%)				
White	160 (74.8)	164 (77.0)	173 (80.8)	497 (77.5)
Black or African American	44 (20.6)	42 (19.7)	38 (17.8)	124 (19.3)
Asian	4 (1.9)	5 (2.3)	1 (0.5)	10 (1.6)
Native Hawaiian or other Pacific Islander	0	0	0	0
American Indian or Alaska Native	2 (0.9)	1 (0.5)	0	3 (0.5)
Other	4 (1.9)	1 (0.5)	2 (0.9)	7 (1.1)

Age is calculated as the rounded down integer value in years of [(Date of consent – Date of Birth)/365.25].
Note: The percentages are based on the number of patients in each treatment group with non-missing data for the parameter.
Note: The 'Total' column summarizes across all treatment groups.
SD standard deviation.
Source: Table 9 at page 66 in Study D3820C00004 Report.

Based upon Table 3.1.1.4.1, the applicant indicated that in general, baseline demographic data were similar across treatment groups. Most patients randomized in this study were White (497 patients; 77.5%), and the mean age of patients was 52.3 years of age. The percentage of participating females was higher than males, and 331 (51.6%) patients had a BMI ⩾30 kg/m^2. There were slightly more males included in the NKTR-118 25 mg group than in the NKTR-118 12.5 mg or placebo treatment groups. The applicant also indicated that baseline demographic data were comparable across treatment groups by baseline laxative response status (i.e., LIR and non-LIR).

Finally, the applicant emphasized that in overall, the mean Cpez!Nbtt!Joefy!)BMI) was similar across treatment groups: 31.6, 32.1, and 31.3 kg/m^2 in the NKTR-118 25 mg, 12.5 mg, and placebo groups, respectively.

3.1.1.5 Applicant's Efficacy Analysis Results and Conclusions

The applicant indicated that all efficacy analyses were performed using their ITT population. The primary and key secondary efficacy variables were analyzed based upon the proposed Multiple Testing Procedure (MTP). The MTP method controls the two-sided overall type I error rate in the strong sense at 0.05 by comparing two doses of 12.5 mg and 25 mg versus placebo each at two-sided significance level of 0.025. Then, within each dose group comparing to placebo, there was a pre-defined fixed-sequence comparisons for the primary and key secondary endpoints. The primary and key secondary endpoints presented below are based upon the order following the proposed hierarchical testing procedure within each dose group comparing to placebo.

The following efficacy analysis results regarding the primary and the key secondary endpoints using ITT population are copied from the original NDA study report. In addition, the sensitivity analyses for the primary and key secondary endpoints using the All Randomized population (defined as randomized population plus patients randomized more than once) reported in the applicant's response document dated 01/10/2014 are briefly summarized since the results from FAS (defined as patients randomized and received at least one dose of study drug) population are similar to that of the All Randomized population.

1) Primary endpoint analysis

A responder (primary endpoint) to study drug during Weeks 1 to 12 was defined as a patient with at least 3 SBMs/week and at least a one SBM/week increase over baseline for at least 9 out of the 12 treatment weeks and 3 out of the last 4 treatment weeks during the double-blind treatment period. The result of the primary endpoint analysis was demonstrated by the primary analysis using the ITT analysis set. Table 3.1.1.5.1 presents the efficacy analysis results for the primary endpoint.

Table 3.1.1.5.1 (Applicant's) Efficacy comparisons assessed by response rate for Weeks 1 to 12 using the ITT population - Study D3820C00004

Treatment Group	n	Number (%) of patients responding	Comparison versus Placebo [a]		
			RR	95% CI	p-value
Placebo	214	63 (29.4)	NA	NA	NA
NKTR-118 12.5 mg	213	87 (40.8)	1.380	(1.062, 1.795)	0.015 *
NKTR-118 25 mg	214	95 (44.4)	1.509	(1.168, 1.949)	0.001 *

* Statistically significant under the multiple testing procedure.
a Analysis via Cochran Mantel-Haenszel test stratified by response to laxatives at baseline (LIR, LAR, LUR).
Note: Response rate is based on the number of patients in the ITT analysis set in each treatment group.
CI confidence interval; CMH Cochran Mantel-Haenszel; ITT intent-to-treat;
NA Not applicable; RR Relative risk (a relative risk >1 is indicative of higher response rate on the NKTR-118 arm).
Source: Table 14 at page 80 in Study D3820C00004 Report.

Based upon Table 3.1.1.5.1, the applicant indicated that for the primary efficacy variable, there was a statistically significantly higher response rate in the NKTR-118 25 mg and 12.5 mg groups when compared with placebo over 12 weeks in patients with OIC. The response rates were 44.4% for NKTR-118 25 mg, 40.8% for NKTR-118 12.5 mg, and 29.4% for placebo. The response rates were 15.0 percentage points and 11.4 percentage points numerically higher in the NKTR-118 25 mg and 12.5 mg groups, respectively, compared with placebo.

In addition, the results of the primary endpoint analyses reported by the applicant in the response document dated 01/10/2014 using the All-Randomized population also show that the response rates for both NKTR-118 25 mg (45.0%) and 12.5 mg (41.0%) groups were significantly higher than that of placebo (30.0%).

2) Key secondary endpoint analysis

- Response to study drug in the LIR subgroup during Weeks 1 to 12

The results for the response to study drug in the LIR subgroup are summarized in Table 3.1.1.5.2.

Table 3.1.1.5.2 (Applicant's) - Response rate for Weeks 1 to 12 in the LIR subgroup using the ITT population - Study D3820C00004

Treatment Group	n	Number (%) of patients responding	Comparison versus Placebo [a]		
			RR	95% CI	p-value
Placebo	118	34 (28.8)	NA	NA	NA
NKTR-118 12.5 mg	115	49 (42.6)	1.479	(1.038, 2.107)	0.028 *
NKTR-118 25 mg	117	57 (48.7)	1.691	(1.205, 2.373)	0.002 *

* Statistically significant under the multiple testing procedure.
[a] Analysis via Chi square test.
Note: Response rate is based on the n in the individual treatment group in the LIR subgroup.
CI confidence interval; LIR Laxative Inadequate Responder/Response; NA Not applicable; RR Relative risk.
Source: Table 16 at page 85 in Study D3820C00004 Report.

Based upon Table 3.1.1.5.2, the applicant indicated that in the LIR subgroup, under multiplicity adjustment procedure, there was a statistically significantly higher response rate in the NKTR-118 25 mg and 12.5 mg groups compared with placebo over 12 weeks in patients with OIC. The response rates were 48.7% for NKTR-118 25 mg, 42.6% for NKTR-118 12.5 mg, and 28.8% for placebo. The response rates were 19.9 percentage points and 13.8 percentage points higher in the NKTR-118 25 mg and 12.5 mg groups, respectively, compared with placebo.

In addition, the analyses assessed by the response rate for patients in the LIR subgroup reported by the applicant in the response document using the All-Randomized population also show that the response rates for both NKTR-118 25 mg (48.7%) and 12.5 mg (43.1%) groups were significantly higher than that of placebo (29.2%).

- Time (in hours) to first post-dose laxation without using rescue laxatives within 24 hours

The Kaplan-Meier estimates of the median times to the first post-dose SBM (laxation without the use of rescue laxatives in the previous 24 hours) for three treatment groups are presented in Table 3.1.1.5.3.

Table 3.1.1.5.3 (Applicant's) Time in hours to first post-dose SBM using the ITT population - Study D3820C00004

Treatment Group	n	Median time to first SBM in hours[a] (95% CI)	P-value (Log Rank Test)
Placebo (P)	214	35.8 (27.0, 48.1)	
Movantik 12.5 mg (M)	213	20.4 (11.5, 22.7)	< 0.001*
Movantik 25 mg (M)	214	5.9 (4.8, 11.5)	< 0.001*

a: Estimates calculated using the Kaplan-Meier technique.
Note: The percentages are based on the number of ITT patients in each treatment group.
CI confidence interval; ITT intent-to-treat; SBM spontaneous bowel movement.
Source: Table 17 at page 89 in Study D3820C00004 Report.

Based upon Table 3.1.1.5.3, the applicant indicated that the NKTR-118 25 mg and 12.5 mg groups had shorter median time to first post-dose SBM compared with placebo (5.9, 20.4, and 35.8 hours, respectively). In addition, the time to first post-dose SBM was significantly shorter for both the NKTR-118 25 mg and NKTR-118 12.5 mg groups compared with placebo using the log-rank test stratified by response to laxatives at baseline.

Finally, the analyses reported by the applicant in the response document using the All-Randomized population also show that the time to first post-dose SBM for both of the NKTR-118 25 mg and 12.5 mg groups was significantly shorter than that of placebo.

- Mean number of days per week with at least one SBM during Weeks 1 to 12

The efficacy comparisons assessed by the mean number of days per week with at least one SBM during Weeks 1 to 12 is presented in Table 3.1.1.5.4.

Table 3.1.1.5.4 (Applicant's) Repeated measures analysis of change from baseline in mean number of days per week with at least 1 SBM using ITT population - Study D3820C00004

Time point	Treatment Group	n	LS Means (SEM)	Difference versus Placebo [a]		
				LS Mean	95% CI	p-value
Weeks 1 to 12	Placebo	211	1.66 (0.13)	NA	NA	NA
	NKTR-118 12.5 mg	211	2.21 (0.13)	0.55	(0.24, 0.86)	<0.001 *
	NKTR-118 25 mg	212	2.48 (0.13)	0.82	(0.51, 1.13)	<0.001 *

*Statistically significant under the multiple testing procedure.
[a] Analysis via MMRM (Mixed Model for Repeated Measurement) with fixed effects for baseline, baseline laxative response, treatment and treatment time interaction. Study pooled center is included as a random effect.
Note: Patient is included in the repeat statement, and an unstructured covariance matrix has been assumed.
Note: Baseline value used to calculate LS Means=1.35.
Note: Mean number of days per week with at least 1 SBM is a key secondary endpoint included in the multiple testing procedure.
Note: All patients with evaluable data at both baseline and at least 1 post-baseline week are included in the analysis.
CI Confidence Interval; LS Mean Least-Squares Mean, estimated via the contrast statement in PROC MIXED;
NA Not applicable; SBM spontaneous bowel movement; SEM Standard error of the mean.
Source: Table 18 at page 91 in Study D3820C00004 Report.

Based upon Table 3.1.1.5.4, the applicant indicated that over weeks 1 to 12, change from baseline in mean number of days/week with at least one SBM for NKTR-118 25 mg and NKTR-118 12.5 mg were significantly higher than that of placebo.

In addition, the analyses reported by the applicant in the response document using the All-Randomized population also show that change from baseline in mean number of days/week with at least one SBM for both of the NKTR-118 groups were significantly higher than that of placebo.

3.1.1.6 Statistical Reviewer's Analysis and Comments

In order to validate the applicant's claim on the superiority of Movantik (NKTR-118) to placebo, this reviewer performs two analyses based upon the primary endpoint (response rate during 12-week treatment period): 1) efficacy comparison by center and 2) sensitivity analysis with certain centers removed. Then, this reviewer makes comments on the efficacy strength of Movantik.

Statistical Reviewer's Analysis

i) Efficacy comparison by center

In the efficacy comparison by center, this reviewer compares the efficacy of Movantik versus placebo based upon the response rate during 12-week treatment period. Since Study D3820C00005 failed to show that the response rate of Movantik 12.5 mg was significantly higher than that of placebo assessed by the primary endpoint, the efficacy comparisons by center are focused on high dose (Movantik 25 mg). The results for low dose (Movantik 12.5 mg) presented here are for information / completeness. Data used in this analysis was submitted through original NDA supplement dated 09/16/2013.

Due to small centers without capability to dominate the superiority of Movantik to placebo, in this efficacy analysis, centers with numbers of patients enrolled no less than twelve are explored and the result is presented in Table 3.1.1.6.1.

Table 3.1.1.6.1 (Reviewer's) Response rate by center during the 12-week treatment period using the ITT population - Study D3820C00004

CENTER NUMBER	PLACEBO (P) % (N/N)	MOVANTIK 12.5 MG (ML) % (N/N)	MOVANTIK 25 MG (MH) % (N/N)	DIF (12.5 ML – P) % (N/N)	DIF (25 MH – P) % (N/N)
4003	30.0% (3/10)	50.0% (1/2)	23.1% (3/13)	20.0%	-6.9%
4021	16.7% (1/6)	20.0% (1/5)	0.0% (0/2)	3.3%	-16.7%
4022	28.6% (2/7)	16.7% (1/6)	--------	-1.9%	-------
4026	**16.7% (1/6)**	**25.0% (2/8)**	**66.7% (2/3)**	**8.3%**	**50.0%**
4033	30.0% (3/10)	33.3% (2/6)	33.3% (3/9)	3.3%	3.3%
4036	75.0% (3/4)	50.0% (3/6)	0.0% (0/2)	-25.0%	-75.0%
4042	20.0% (1/5)	33.3% (1/3)	25.0% (1/4)	13.3%	5.0%
4053	**0.0% (0/5)**	**14.3% (1/7)**	**50.0% (1/2)**	**14.3%**	**50.0%**
4054	**0.0% (0/5)**	**50.0% (2/4)**	**40.0% (2/5)**	**50.0%**	**40.0%**
4056	22.2% (2/9)	25.0% (3/12)	44.4% (4/9)	2.8%	22.2%
4061	**0.0% (0/4)**	**50.0% (3/6)**	**37.5% (3/8)**	**50.0%**	**37.5%**
4062	42.9% (3/7)	0.0% (0/1)	50.0% (2/4)	-42.9%	7.1%
4068	23.5% (4/17)	23.1% (3/13)	16.7% (2/12)	-0.4%	-6.8%
4071	**57.1% (4/7)**	**37.5% (3/8)**	**100.0% (2/2)**	**-19.6%**	**42.9%**
4074	0.0% (0/3)_	50.0% (2/4)	20.0% (1/5)	50.0%	20.0%
4083	44.4% (4/9)	50.0% (8/16)	66.7% (8/12)	5.6%	22.3%
Total	29.4% (63/214)	40.8% (87/213)	44.4% (95/214)	11.4%	15.0%

Based upon the results from Table 3.1.1.6.1, although the response rates for the five centers (4026, 4053, 4054, 4061, and 4071) for Movantik 25 mg are more than 35% greater than that of placebo, the sizes of the rate differences between Movantik 25 mg versus placebo across centers seem to be evenly distributed in the range of -75.0% to 50.0%. No center is deemed to have abnormally large effect size to dominate the superiority of Movantuk 25 mg to placebo. However, in order to explore the impact of the five centers to the superiority of Movantik 25 mg to placebo, this reviewer performs the sensitivity analysis by deleting data from these centers.

Since for the four centers (4026, 4053, 4054, and 4701), each with small number of patients (less than or equal to five) enrolled in the Movantik 25 mg group, these four centers are not considered to have impact on the superiority of Movantik 25 mg to placebo. Accordingly, this reviewer performed a sensitivity analysis by deleting center 4061 to assess the impact of this center to the superiority of Movantik 25 mg to placebo.

ii) Sensitivity analysis

In order to assess the impact of center 4061 on the superiority of Movantik 25 mg to placebo assessed by the primary endpoint, this reviewer applies Cochran-Mantel-Haenszel (CMH) tests stratified by the response to laxatives at baseline (applicant's method) for efficacy comparisons after deleting center 4061.

The result of the responder rate analysis is presented by Table 3.1.1.6.2.

Table 3.1.1.6.2 (Reviewer's) Efficacy comparison assessed by response rate during the 12-week treatment period using the ITT population after deleting center 4061 - Study D3820C00004

Treatment Group	n	Number (%) of Patients Responding	Movantik versus Placebo[a] % Difference	P-value
Placebo (P)	210	63 (40.7%)	NA	
Movantik 12.5 mg (M)	207	84 (57.1%)	16.4%	0.026
Movantik 25 mg (M)	206	92 (59.4%)	18.7%	0.002

a Analysis via Cochran Mantel-Haenszel test stratified by response to laxatives at baseline (LIR, LAR, LUR).
Note: Response rate is based on the number of patients in the ITT analysis set in each treatment group.

Table 3.1.1.6.2 indicates that after excluding patients from center 406, the study response rate during the12-week treatment period, for the Movantik 25 mg group, remained significantly greater than that of placebo. Accordingly, the efficacy strength of Movantik 25 mg to placebo is deemed not to have been dependent on particular centers.

Statistical Reviewer's Comments on the Efficacy of Movantik

As mentioned in the sub-section 2.1, the Agency issued an information request letter (dated 12/20/2013) to the applicant. The applicant's response document was received on January 10, 2014. Accordingly, the comments given below on the strength of Movantik are based upon the original NDA submission, the response document, and analysis results performed by this reviewer.

Although Movantik 12.5 mg showed a significantly better result than placebo in Study D3820C00004, it failed to do so in Study D3820C00005. Consequently, the efficacy of Movantik 12.5 mg was not demonstrated in two trials, and, moreover, (b) (4) Thus the following comments on the effects of Movantik apply only to Movantik 25mg.

Comments on the Primary Endpoint

- The response rate assessed by the primary endpoint in the Movantik 25 mg was significantly higher than that of placebo using the applicant's ITT population as defined in the original NDA application. The therapeutic gain of Movantik 25 mg versus placebo was 15.0%.

- Based upon the Applicants' response document dated 01/10/2014, the efficacy comparisons of Movantik 25 mg versus placebo assessed by the primary endpoint using the All Randomized and FAS populations also showed positive results in favor of Movantik.

- From this reviewer's sensitivity analysis based upon the primary endpoint, the response rate differences between Movantik 25 mg and placebo were evenly distributed across

centers, and no center is deemed to have abnormally large rate difference to dominate the superiority of Movantik 25 mg versus placebo.

Comments on the Key Secondary Endpoints

- The efficacy comparisons of Movantik 25 mg versus placebo assessed by following three key secondary endpoint analyses performed by the applicant from original NDA submission show positive results in favor of Movantik:

  i) Response to study drug in the LIR subgroup during Weeks 1 to 12;
  ii) Time (in hours) to first post-dose laxation without using rescue laxatives within 24 hour;
  iii) Mean number of days per week with at least one SBM during Weeks 1 to 12.

- In addition, based upon the response document dated 01/10/2014, the efficacy comparisons of Movantik 25 mg versus placebo assessed by the three key secondary endpoints performed by the applicant using the All Randomized and FAS populations also show positive in favor of Movantik.

- Finally, the non-parametric analysis reported by the response document supports the findings of the protocol-specified Mixed Model for Repeated Measures (MMRM) analyses for Mean number of days per week with at least one SBM during Weeks 1 to 12.

Accordingly, this reviewer's analyses and the data submitted by the applicant support the efficacy of Movantik 25 mg assessed by the primary and the key secondary endpoints.

3.1.2 Study D3820C00005

3.1.2.1 Design and Endpoints

The primary objective and study design (including primary and key secondary endpoints) of this study were the same as that of Study D3820C00004. For detail of the primary objective and study design, please refer to Sub-section 3.1.1.1. This study was conducted in the U.S., Belgium, Croatia, Czech Republic, Hungary, Spain, Sweden, and the United Kingdom.

3.1.2.2 Statistical Methodologies

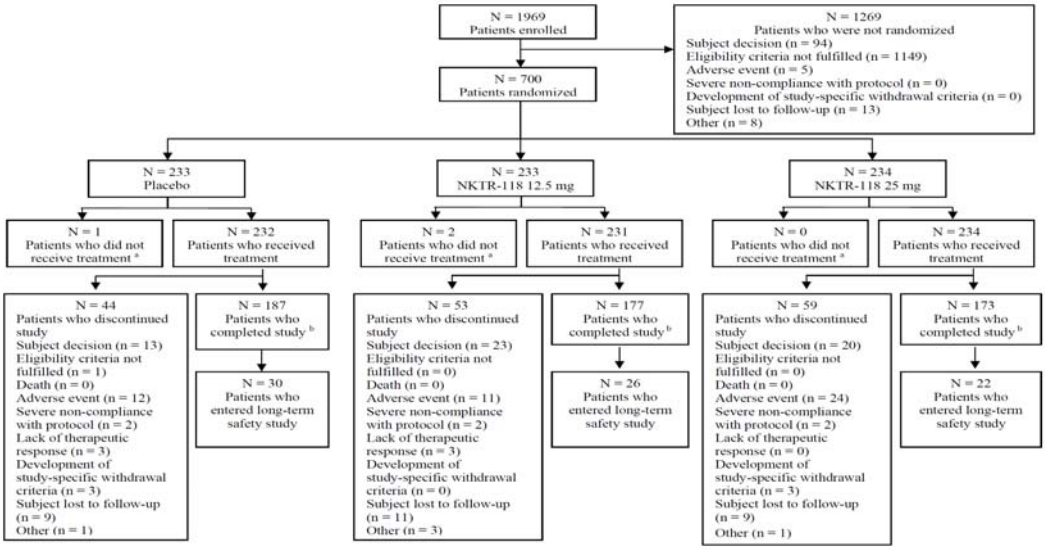
The statistical analysis methods (including study analysis sets) of this study were the same as that of Study D3820C00004. For detail, refer to Sub-section 3.1.1.2.

3.1.2.3 Patient Disposition

The first subject was enrolled on 3/28/2011, and the last subject completed the study on

9/20/2012. The disposition of the patients in this study (which consisted of up to a 2-week screening period, a 2-week OIC confirmation period, and a 12-week treatment period) is summarized in Figure 3.1.2.3.1.

Figure 3.1.2.3.1 (Applicant's)Summary of subject disposition - Study D3820C00005



[a] Randomized patients did not receive treatment included eligibility criteria not fulfilled (1 patient each in the placebo and NKTR-118 12.5 mg groups), and subject decision (1 patient in the NKTR-118 12.5 mg group).
[b] A total of 4 patients who received treatment (2 patients in the NKTR-118 25 mg group and 1 patient each in the NKTR-118 12.5 mg and placebo groups) had been previously randomized within the NKTR-118 program at a different study center. These patients are included in the number of patients who received treatment but were excluded from the ITT and Safety analysis sets and are therefore not included as patients who completed the study
Source: Figure 2 at page 62 in Study D3820C00005 Report.

The applicant indicated that a total of 1969 patients entered screening. 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. Patients who did not enter the long-term safety study were to participate in a follow-up visit 2 weeks after the last dose of study drug. Overall, 78 patients from the ITT analysis set (11.1% of the total randomized) completed the study and continued into long-term safety study D3820C00008.

A total of 4 additional patients (2 patients in the NKTR-118 25 mg group and 1 patient each in the NKTR-118 12.5 mg and placebo groups) received treatment, but had previously or concurrently participated in the NKTR-118 program at another study center. Three of these patients (0.4%; 1 patient in each treatment group) completed the study. These 4 patients were identified prior to database lock and were not included in the ITT or Safety analysis sets. The remaining text in this section describes the patients in the ITT analysis set; however, percentages are based on the total number of patients randomized.

The following patients were randomized but did not receive treatment: two patients due to eligibility criteria not fulfilled (patient E5297017 in the placebo group and patient E5262012 in

the NKTR-118 12.5 mg group) and one patient (E5565001) due to subject decision in the NKTR-118 12.5 mg group. These patients were not included in the mITT, PP, or the Safety analysis sets, but were included in the primary ITT analysis set.

A total of 696 patients from 117 centers across the following eight countries were randomized and included in the ITT analysis set: Belgium (7 patients; 1.0%), Croatia (8 patients; 1.1%), Czech Republic (10 patients; 1.4%), Hungary (14 patients; 2.0%), Spain (15 patients; 2.2%), Sweden (2 patients; 0.3%), United Kingdom (4 patients; 0.6%), and the US (636 patients; 91.4%).

The analysis sets and the number of patients in each analysis set are summarized in Table 3.1.2.3.1. The applicant indicated that all decisions on the inclusion or exclusion of patients from analyses were made while the data were still blinded.

The analysis sets and the number of patients in each analysis set are summarized in Table 3.1.2.3.1. The applicant indicated that all decisions on the inclusion or exclusion of patients from analyses were made while the data were still blinded. Additional analysis sets (not shown in the table) were defined by the reviewer in the Agency IR as the All Randomized population (all randomized including 4 patients who were randomized multiple times) and the FAS population (all randomized who received study drug).

Table 3.1.2.3.1 (Applicant's) Summary of analysis sets - Study D3820C00005

	Number of patients			
	Placebo (N = 233)	**NKTR-118 12.5 mg (N = 233)**	**NKTR-118 25 mg (N = 234)**	**Total (N = 700)**
All randomized patients	233	233	234	700
Intent-to-treat analysis set	232	232	232	696
Patients excluded from intent-to-treat set	1	1	2	4
Modified Intent-to-treat analysis set	231	228	226	685
Patients excluded from modified intent-to-treat set	2	5	8	15
Patients included in per-protocol analysis set	213	213	223	649
Patients excluded from per-protocol analysis set	20	20	11	51
Patients included in Safety analysis set	231	230	232	693
Patients excluded from Safety analysis set	2	3	2	7

Note: For the Safety analysis set data are summarized according to treatment first received. For all other analysis sets, data are summarized by randomized treatment.
Note: The ITT analysis set includes the all randomized patients excluding patients who were randomized multiple times at different centers.
Note: The mITT analysis set includes all ITT patients who received at least 1 dose of IP (NKTR-118 or placebo) and had at least 1 post-baseline efficacy assessment.
Note: The PP analysis set includes only those ITT patients who have no important protocol deviations and who received the treatment to which they were randomized.
IP investigational product; ITT intent-to-treat; mITT modified intent-to-treat; PP per-protocol.
Source: Table 8 at page 66 in Study D3820C00005 Report.

Based upon Table 3.1.2.3.1, the applicant indicated that there were at least 210 patients per treatment group in each analysis set, which was the planned number for randomized patients per treatment group. A similar number of patients across treatment groups were included in the ITT, mITT, and Safety analysis sets. Fewer patients in the NKTR-118 25 mg group (11 patients) were excluded from the PP analysis set compared with the number of patients in the NKTR-118 12.5 mg and placebo groups (20 patients each) who were excluded.

This study randomized an additional 70 patients above the protocol target of 630. Within the final days of recruitment, more patients signed informed consent and were categorized as eligible for the study, than had been anticipated by the study team. Recruitment was closed according to applicable procedures, and patients who had already signed consent at the time enrollment was closed were permitted to be randomized if they met all inclusion and exclusion criteria.

3.1.2.4 Demographics and Baseline Characteristics

The demographic and key baseline characteristics of study patients are summarized in Table 3.1.2.4.1.

Table 3.1.2.4.1 (Applicant's) Demographic characteristics (Intent-to-treat analysis set) - Study D3820C00005

Demographic characteristics	Placebo (N = 232)	NKTR-118 12.5 mg (N = 232)	NKTR-118 25 mg (N = 232)	Total (N = 696)
Age (years) [a]				
n	232	232	232	696
Mean	52.3	52.0	51.9	52.1
SD	11.62	11.02	12.11	11.58
Median	53.0	52.0	53.0	52.5
Min	21	21	19	19
Max	80	82	80	82
Age group (years), n (%)				
Age <50	94 (40.5)	96 (41.4)	84 (36.2)	274 (39.4)
≥50 to <65	110 (47.4)	110 (47.4)	115 (49.6)	335 (48.1)
≥65 to <75	23 (9.9)	19 (8.2)	26 (11.2)	68 (9.8)
≥75	5 (2.2)	7 (3.0)	7 (3.0)	19 (2.7)
Body mass index (BMI) (kg/m^2)				
<18.5	3 (1.3)	3 (1.3)	2 (0.9)	8 (1.1)
18.5-<30	118 (50.9)	123 (53.0)	112 (48.3)	353 (50.7)
≥30	111 (47.8)	106 (45.7)	115 (49.6)	332 (47.7)
Sex, n (%)				
Male	87 (37.5)	83 (35.8)	85 (36.6)	255 (36.6)
Female	145 (62.5)	149 (64.2)	147 (63.4)	441 (63.4)
Race, n (%)				
White	183 (78.9)	187 (80.6)	189 (81.5)	559 (80.3)
Black or African American	44 (19.0)	41 (17.7)	40 (17.2)	125 (18.0)
Asian	0	1 (0.4)	0	1 (0.1)
Native Hawaiian or other Pacific Islander	0	0	1 (0.4)	1 (0.1)
American Indian or Alaska Native	2 (0.9)	1 (0.4)	1 (0.4)	4 (0.6)
Other	3 (1.3)	2 (0.9)	1 (0.4)	6 (0.9)

[a] Age is calculated as the rounded down integer value in years of [(Date of consent – Date of Birth)/365.25].
Note: The percentages are based on the number of patients in each treatment group with non-missing data for the parameter.
Note: The 'Total' column summarizes across all treatment groups; SD: standard deviation.
Source: Table 9 at page 68 in Study D3820C00005 Report.

Based upon Table 3.1.2.4.1, the applicant indicated that baseline demographic data were comparable across treatment groups by baseline laxative response status (i.e., LIR and non-LIR). A total of 83.0% of the LIR and 77.3% of the non-LIR patients were White. The mean age was 53.2 years (ranging from 21 to 81 years) for the LIR group and 50.7 years (ranging from 19 to 82 years) for the non-LIR group. Similar to the overall population, the percentage of participating females was higher than males in both LIR and non-LIR groups and more than 45% of patients had a BMI $\geqslant$30 kg/m^2 in both the LIR and non-LIR group.

3.1.2.5 Applicant's Efficacy Analysis Results and Conclusions

All efficacy analyses were performed using the applicant's ITT population. The primary and the key secondary efficacy variables were analyzed based upon the proposed Multiple Testing Procedure (MTP). The MTP method controls the two-sided overall type I error rate at 0.05 in the strong sense by comparing two doses of 12.5 mg and 25 mg versus placebo each at two-sided significance level of 0.025. Then, within each dose group comparing to placebo, there was a pre-defined fixed-sequence comparisons for the primary and key secondary endpoints. The primary and key secondary endpoints presented below are based upon the order following the proposed hierarchical testing procedure within each dose group comparing to placebo.

The following efficacy analysis results regarding the primary and the key secondary endpoints are copied from the original NDA study report. In addition, the sensitivity analyses for the primary and key secondary endpoints using the FAS (defined as patients randomized and who received at least one dose of study drug) and the All Randomized population (defined as all randomized population including patients randomized more than once) reported in the applicant's response document dated 01/10/2014 are briefly discussed. The results using the FAS population are similar to that for the All Randomized population and not discussed.

1) Primary endpoint analysis

A responder to study drug during Weeks 1 to 12 was defined as a patient with at least 3 SBMs/week and at least a one SBM/week increase over baseline for at least 9 out of the 12 treatment weeks and 3 out of the last 4 treatment weeks during the double-blind treatment period. The applicant's result of the primary endpoint analysis was based on the primary analysis data set (ITT population).

Table 3.1.2.5.1 presents the applicant's efficacy analysis results.

Table 3.1.2.5.1 (Applicant's) Efficacy comparisons assessed by response rate for Weeks 1 to 12 using the ITT population - Study D3820C00005

Treatment Group	n	Number (%) of patients responding	Comparison versus Placebo [a]		
			RR	95% CI	p-value
Placebo	232	68 (29.3)	NA	NA	NA
NKTR-118 12.5 mg	232	81 (34.9)	1.188	(0.911,1.548)	0.202
NKTR-118 25 mg	232	92 (39.7)	1.348	(1.045,1.739)	0.021*

* Statistically significant under the multiple testing procedure.
a Analysis via Cochran Mantel-Haenszel test stratified by response to laxatives at baseline (LIR, LAR, LUR).
Note: Response rate is based on the number of patients in the ITT analysis set in each treatment group.
CI confidence interval; CMH Cochran Mantel-Haenszel; ITT intent-to-treat; LAR Laxative Adequate Responder/Response; LIR Laxative Inadequate Responder/Response; LUR Laxative Unknown Responder/Response; NA Not applicable; RR Relative risk (a relative risk >1 is indicative of higher response rate on the NKTR-118 arm).
Source: Table 14 at page 82 in Study D3820C00005 Report.

Based upon Table 3.1.2.5.1, the applicant indicated that for the primary efficacy variable, there was a statistically significantly higher response rate in the Movantik (NKTR-118) 25 mg group (39.7%) compared with placebo (29.3%) over the 12 weeks in patients with OIC. However, there was no statistically significant difference between the 12.5 mg group (34.9%) and placebo. The response rate over 12 weeks was 10.4 percentage points and 5.6 percentage points higher in the NKTR-118 25 mg and 12.5 mg groups, respectively, compared with placebo.

In addition, the result of the primary endpoint analyses reported by the applicant in the response document using the All-Randomized population also showed that the response rate for the Movantik 25 mg group (39.7%) was significantly higher than that of placebo (29.2%).

2) Key secondary endpoint analysis

- Response to study drug in the LIR subgroup during Weeks 1 to 12

The result for the response to study drug in the LIR subgroup is summarized in Table 3.1.2.5.2.

Table 3.1.2.5.2 (Applicant's) Response rate for Weeks 1 to 12 in the LIR subgroup using the ITT population - Study D3820C00005

Treatment Group	n	Number (%) of patients responding	Comparison versus Placebo [a]		
			RR	95% CI	p-value
Placebo	121	38 (31.4)	NA	NA	NA
NKTR-118 12.5 mg	125	53 (42.4)	1.350	(0.967, 1.884)	0.074
NKTR-118 25 mg	124	58 (46.8)	1.489	(1.078, 2.058)	0.014 *

* Statistically significant under the multiple testing procedure.
[a] Analysis via Chi square test.
Note: Response rate is based on the n in the individual treatment group in the LIR subgroup.
Note: Response rate over Weeks 1 to 12 in the LIR subgroup is a key secondary endpoint included in the multiple testing procedure.
CI confidence interval; LIR Laxative Inadequate Responder/Response; NA Not applicable; RR Relative risk (a relative risk >1 is indicative of higher response rate on the NKTR-118 arm).
Source: Table 16 at page 87 in Study D3820C00005 Report.

Based upon Table 3.1.2.5.2, the applicant indicated that in the LIR subgroup, there was a statistically significantly higher response rate in the NKTR-118 25 mg group compared with placebo (46.8% vs. 31.4%) over 12 weeks in patients with OIC. However, there was no statistically significant difference between the 12.5 mg group (42.4%) and placebo. The response rate over 12 weeks was 15.4 percentage points and 11 percentage points higher in the NKTR-118 25 mg and 12.5 mg groups, respectively, compared with placebo.

Similar to the results of ITT population, the analysis result of the All Randomized population assessed by the response rate for patients in the LIR subgroup also shows that the response rate of Movantik (NKTR-118) 25 mg group as significantly higher than that of placebo (47.2% vs. 31.4%).

- Time (in hours) to first post-dose laxation without using rescue laxatives within 24 hours

The Kaplan-Meier estimates of the median times to the first post-dose SBM (laxation without the use of rescue laxatives in the previous 24 hours) for three treatment groups are presented in Table 3.1.2.5.3.

Table 3.1.2.5.3 (Applicant's) Time in hours to first post-dose SBM using ITT population - Study D3820C00005

Treatment Group	n	Median time to first SBM in hours[a] (95% CI)	P-value (Log Rank Test)
Placebo (P)	232	37.2 (30.0, 46.9)	
NKTR-118 12.5 mg (M)	232	19.3 (9.4, 22.3)	< 0.001
NKTR-118 25 mg (M)	232	12.0 (7.0, 21.5)	< 0.001*

[a]: Estimates calculated using the Kaplan-Meier technique.
Note: The percentages are based on the number of ITT patients in each treatment group.
CI confidence interval; ITT intent-to-treat; SBM spontaneous bowel movement.
Source: Table 17 at page 91 in Study D3820C00005 Report.

Based upon Table 3.1.2.5.3, the applicant indicated that the NKTR-118 25 mg and 12.5 mg groups had a shorter median time to first post-dose laxation compared with placebo (12.0, 19.3, 37.2 hours respectively). In addition, the time to first post-dose laxation was significantly shorter for both the NKTR-118 25 mg and NKTR-118 12.5 mg groups compared with placebo for both comparisons using the log-rank test stratified by response to laxatives at baseline (LIR, LAR, LUR) based upon ITT population. However, based upon the pre-specified multiple adjustment method, in the absence of a statistically significant difference for the 12.5 mg group primary endpoint, statistical significance shown by this secondary endpoint cannot be claimed.

Finally, the analyses reported by the applicant in the response document using the All-Randomized population also show that time to first post-dose SBM for the Movantik 25 mg is significantly shorter than that of placebo.

- Mean number of days per week with at least 1 SBM during Weeks 1 to 12

The efficacy comparisons assessed by the mean number of days per week with at least one SBM during Weeks 1 to 12 is presented in Table 3.1.2.5.4.

Table 3.1.2.5.4 (Applicant's) Repeated measures analysis of change from baseline in mean number of days per week with at least 1 SBM using ITT population - Study D3820C00005

Time point	Treatment Group	n	LS Means (SEM)	Difference versus Placebo LS Mean	95% CI	p-value[a]
Weeks 1 to 12	Placebo	231	1.73 (0.12)	NA	NA	NA
	NKTR-118 12.5 mg	228	2.12 (0.12)	0.39	(0.09, 0.69)	0.010
	NKTR-118 25 mg	226	2.41 (0.13)	0.68	(0.37, 0.98)	<0.001 *

*Statistically significant under the multiple testing procedure.
[a] Analysis via MMRM (Mixed model for repeated measures) with fixed effects for baseline, baseline laxative response, treatment and treatment time interaction. Study pooled center is included as a random effect.
Note: All patients with evaluable data at both baseline and at least 1 post-baseline week are included in the analysis.
CI Confidence Interval; LS Mean Least-Squares Mean, estimated via the contrast statement in PROC MIXED;
NA Not applicable; SBM spontaneous bowel movement; SEM Standard error of the mean.
Source: Table 18 at page 93 in Study D3820C00005 Report.

Based upon Table 3.1.2.5.4, the applicant indicated that over Weeks 1 to 12, change from baseline in mean number of days/week with at least one SBM for NKTR-118 25 mg was significantly higher than that of placebo. In addition, over Weeks 1 to 12, there was an increase in change from baseline in mean number of days/week with at least one SBM in the Movantik (NKTR-118) 12.5 mg group compared to placebo. However this increase is not considered to be statistically significant under the multiple adjustment procedure.

Finally, the analyses reported by the applicant in the response document using the All-Randomized population also showed that change from baseline in mean number of days/week with at least one SBM for Movantik 25 mg was significantly higher than that of placebo.

3.1.2.6 Statistical Reviewer's Analysis and Comments

In order to validate the applicant's claim on the superiority of Movantik to placebo, this reviewer performs two analyses based upon the primary endpoint (response rate during 12-week treatment period): 1) efficacy comparison by center and 2) a sensitivity analysis excluding centers. Then, this reviewer makes comments on the efficacy strength of Movantik.

Statistical Reviewer's Analysis

i) Efficacy comparison by center

In the efficacy comparison by center, this reviewer compares the efficacy of Movantik versus placebo based upon the response rate during 12-week treatment period. Although the applicant is seeking approval for only the high dose and the efficacy comparison of Movantik 12.5 mg versus placebo performed by the applicant was not significant, the results for both doses are shown here

for completeness.

Centers that enroll only a few subjects do not have capability to dominate the superiority of Movantik to placebo; in this efficacy analysis, only centers with at least 12 patients enrolled were explored and the result is presented in Table 3.1.2.6.1.

Table 3.1.2.6.1 (Reviewer's) Response rate by center during 12-week treatment period using the ITT population - Study D3820C00005

CENTER NUMBER	PLACEBO (P) % (N/N)	MOVANTIK 12.5 MG (ML) % (N/N)	MOVANTIK 25 MG (MH) % (N/N)	DIF (12.5 ML – P) % (N/N)	DIF (25 MH – P) % (N/N)
5205	22.2% (2/9)	13.3% (1/7)	0.0% (0/2)	-8.9%	-22.2%
5206	**0.0% (0/2)**	**25.0% (1/4)**	**62.5% (5/8)**	**25.0%**	**62.5%**
5214	20.0% (1/5)	33.3% (2/6)	25.0% (1/4)	13.3%	5.0%
5215	28.6% (2/7)	33.3% (1/3)	42.9% (3/7)	4.7%	14.3%
5218	**0.0% (0/4)**	**50.0% (3/6)**	**75.0% (6/8)**	**50.0%**	**75.0%**
5220	33.3% (2/6)	75.0% (3/4)	50.0% (1/2)	41.7%	16.7%
5233	33.3% (2/6)	33.3% (1/3)	75.0% (3/4)	0.0%	41.7%
5235	18.2% (2/11)	33.3% (4/12)	28.6% (2/7)	15.1%	10.4%
5236	25.0% (2/8)	33.3% (2/6)	16.7% (2/12)	8.3%	- 8.3%
5237	0.0% (0/4)	0.0% (0/5)	33.3% (1/3)	0.0%	33.3%
5241	20.0% (1/5)	30.0% (3/10)	50.0% (2/4)	10.0%	30.0%
5243	0.0% (0/3)	0.0% (0/3)	20.0% (1/5)	0.0%	20.0%
5246	0.0% (0/3)	33.3% (2/6)	14.3% (1/7)	33.3%	14.3%
5252	66.7% (4/6)	40.0% (2/5)	50.0% (1/2)	-26.7%	-16.7%
5255	50.0% (2/4)	50.0% (2/4)	33.3% (1/3)	0.0%	-16.7%
5267	**22.2% (2/9)**	**60.0% (3/5)**	**75.0% (9/12)**	**37.8%**	**52.8%**
5268	0.0 (0/1)	0.0% (0/4)	37.5% (3/8)	0.0%	37.5%
5273	50.0% (4/8)	37.5% (3/8)	80.0% (4/5)	-12.5%	30.0%
5276	28.6% (2/7)	66.7% (2/3)	0.0% (0/2)	38.1%	-28.6%
5277	33.3% (1/3)	20.0% (1/5)	14.3% (1/7)	-13.3%	-19.0%
5292	100.0% (5/5)	100.0% (5/5)	100.0% (4/4)	0.0%	0.0%
Total	29.3% (68/232)	34.9% (81/232)	39.7% (92/232)	5.6%	10.4%

Based upon the results from Table 3.1.2.6.1, similar to D3820C00004, although the response rates for the three centers (5206, 5218, and 5267) for Movantik 25 mg are more than 50% greater than that of placebo, the sizes of the rate differences between Movantik 25 mg versus placebo across centers seem to be evenly distributed in the range of -28.6% to 75.0%. No centers appear to have abnormally large rate differences to dominate the superiority of Movtantik to placebo.

However, in order to explore the influences of the those three centers to the superiority of Movantik 25 mg to placebo, this reviewer performed a sensitivity analyses by deleting the three centers in the following order: centers 5267, 5218, and finally center 5206.

ii) Sensitivity analysis

First, in order to assess the impact of center 5267, this reviewer applies the Cochran-Mantel-Haenszel (CMH) test stratified by the response to laxatives at baseline (applicant's method) for efficacy comparisons assessed by the primary endpoint after deleting center 5267. The result of

the responder rate analysis is presented by Table 3.1.2.6.2.

Table 3.1.2.6.2 (Reviewer's) Efficacy comparison assessed by response rate during the 12-week treatment period using the ITT population after deleting center 5267- Study D3820C00005

Treatment Group	n	Number (%) of Patients Responding	Movantik versus Placebo[a]	
			% Difference	P-value
Placebo (P)	223	66 (45.8%)	NA	
Movantik 12.5 mg (M)	227	78 (54.2%)	8.4%	0.289
Movantik 25 mg (M)	220	83 (55.7%)	9.9%	0.075

a Analysis via Cochran Mantel-Haenszel test stratified by response to laxatives at baseline (LIR, LAR, LUR).
Note: Response rate is based on the number of patients in the ITT analysis set in each treatment group.

Table 3.1.2.6.2 indicates that the response rate during 12-week treatment period for the Movantik 25 mg group no longer remained significantly greater than that of placebo using ITT population excluding patients from center 5267. Similarly, by separately deleting each of centers 5206 and 5218, the results no longer positive in favor of Movantik 25 mg. Accordingly, by these sensitivity analysis results, one may deem that these three centers played an important role in determining the superiority of Movantik 25 mg to placebo.

Statistical Reviewer's Comments on the Efficacy of Movantik

Since the effect of Movantik 12.5 mg failed to show superiority to placebo assessed by the primary endpoint, the comments on the strength of Movantik apply only to Movantik 25 mg. In addition, as mentioned in the sub-section 2.1 "Overview", in order to address certain concerns, the Agency issued an information request letter to the applicant. Accordingly, the comments given below on are based upon the original NDA submission, the applicant's response document, and analysis results performed by this reviewer.

Comments on the Primary Endpoint

- The response rate assessed by the primary endpoint in the NKTR-118 25 mg was significantly higher than that of placebo based on the ITT population, as performed by the applicant in the original NDA submission. The therapeutic gain of Movantik 25 mg versus placebo was 10.0%.

- Based upon the response document dated 01/10/2014, the efficacy comparisons of Movantik 25 mg versus placebo assessed by the primary endpoint performed by the applicant using the reviewr's All Randomized and FAS populations also show positive results in favor of Movantik.

- Based on the reviewer's site-sensitivity analyses, no center was deemed to have abnormally large rate differences that would dominate the superiority of Movantik. However, the sensitivity analyses performed by deleting individual centers 5206, 5218, and 5267 all showed that the effect of Movantik was no longer statistically significant. Consequently, those 3 centers may have played an important role in determining the superiority of Movantik.

Comments on the Key Secondary Endpoints

- The efficacy comparisons of Movantik 25 mg versus placebo assessed by following three key secondary endpoints analyses performed by the applicant all showed positive results in favor of Movantik:
  i) Response to study drug in the LIR subgroup during Weeks 1 to 12;
  ii) Time (in hours) to first post-dose laxation without using rescue laxatives within 24 hour;
  iii) Mean number of days per week with at least one SBM during Weeks 1 to 12.

- In addition, based upon the response document dated 01/10/2014, the efficacy comparisons of Movantik 25 mg versus placebo assessed by the three key secondary endpoints performed by the applicant using the All Randomized and FAS populations showed similar, positive results in favor of Movantik.

- Finally, the non-parametric analysis reported by the response document supports the findings of the protocol-specified Mixed Model for Repeated Measures (MMRM) analyses for Mean number of days per week with at least one SBM during Weeks 1 to 12.

Accordingly, this reviewer's analyses as well as the data submitted by the applicant support the efficacy of Movantik 25 mg assessed by the primary and the key secondary endpoints.

3.2 Evaluation of Safety

3.2.1 Study D3820C00004

The applicant indicated that more patients in the Movantik (NKTR-118) 25 mg group were reported to have at least one AE compared with the NKTR-118 12.5 mg and placebo groups. A total of 131 (61.2%), 104 (49.3%), and 100 (46.9%) patients in the NKTR-118 25 mg, 12.5 mg and placebo groups, respectively, were reported to have at least one AE.

There were two deaths during the study, both of which occurred during the follow-up period. Two patients in the NKTR-118 12.5 mg group were reported to have fatal AEs (non-small cell lung cancer and cardiac valve replacement complication). Neither death was considered by the principal investigator (PI) to be related to investigational product (IP).

A total of 7 (3.3%), 11 (5.2%), and 11 (5.2%) patients in the NKTR-118 25 mg, 12.5 mg, and placebo groups, respectively, were reported to have at least one SAE.

Finally, the present study was designed to randomize a minimum of 50% of study patients who were laxative inadequate responder (LIR). The safety summarized by the applicant according to the baseline laxative response status (LIR versus non-LIR) is given below.

- The frequencies of AEs in any category during the randomized treatment and follow-up

periods for patients categorized as LIR and non-LIR at baseline were generally comparable with the overall safety analysis set.

- In both subgroups (LIR and non-LIR), more patients in the NKTR-118 25 mg group were reported to have at least one AE compared with the NKTR-118 12.5 mg and placebo groups.
- Of the two deaths during the study, one occurred in the LIR subgroup (cardiac valve replacement complication) and one occurred in the non-LIR subgroup (non-small cell lung cancer).
- In both subgroups (LIR and non-LIR), more patients in the NKTR-118 25 mg group discontinued IP due to an AE compared with the NKTR-118 12.5 mg and placebo groups.

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3.2.2 Study D3820C00005

The applicant indicated that more patients in the Movantik (NKTR-118) 25 mg group were reported to have at least one AE compared with the NKTR-118 12.5 mg and placebo groups. A total of 160 (69.0%), 137 (59.6%), and 136 (58.9%) patients in the NKTR-118 25 mg, 12.5 mg, and placebo groups, respectively, were reported to have at least one AE.

Among the common AEs (ie, those preferred terms reported in ⩾2% of patients in any treatment group), six AEs were reported in more than 5% of patients in either of the NKTR-118 treatment groups and in double, or more, than the percentage of patients in the placebo group: abdominal pain, diarrhea, nausea, vomiting, flatulence, and back pain

There were no deaths during the study.

A total of 8 (3.4%), 14 (6.1%), and 12 (5.2%) patients in the NKTR-118 25 mg, 12.5 mg, and placebo groups, respectively, were reported to have at least one serious adverse events (SAE). The applicant further indicated that the frequency and types of SAEs during the treatment period were similar across treatment groups. A total of 8 (3.4%), 14 (6.1%), and 12 (5.2%) patients in the NKTR-118 25 mg, 12.5 mg, and placebo groups, respectively, were reported to have at least one SAE during the study. Except for accidental overdose (0.9%) in the NKTR-118 12.5 mg group, no other preferred term was reported as a SAE for NKTR-118. One patient in the placebo group had a SAE of acute myocardial infarction and one patient in the placebo group had a SAE of angina pectoris during the study.

In addition, a higher proportion of patients in the NKTR-118 25 mg group discontinue IP due to an AE compared with the NKTR-118 12.5 mg and placebo groups. A total of 24 (10.3%), 12 (5.2%), and 12 (5.2%) patients in the NKTR-118 25 mg, 12.5 mg, and placebo groups, respectively, discontinued IP due to an AE.

Finally, the present study was designed to randomize a minimum of 50% of study patients who were laxative inadequate responder (LIR). The safety summarized by the applicant according to the baseline laxative response status (LIR versus non-LIR) is given below.

- The frequencies of AEs in any category during the randomized treatment and follow-up periods for patients categorized as LIR and non-LIR at baseline were generally comparable with the overall safety analysis set.
- In both subgroups (LIR and non-LIR), more patients in the NKTR-118 25 mg group were reported to have at least one AE, as well as discontinuation of IP due to an AE!(DAEs), compared with the NKTR 118 12.5 mg and placebo groups.
- Among the common AEs in the LIR and non-LIR subgroups (i.e., those preferred terms reported in ⩾2% of patients in any treatment group), the following AEs were reported in more than 5% of patients in either of the NKTR-118 treatment groups and in double, or more, than the percentage of patients in the placebo group: abdominal pain, diarrhoea, nausea, and flatulence in the LIR subgroup; and abdominal pain and vomiting in the non-LIR subgroup.

4.0 SUBGROUP ANALYSIS

4.1 Gender, Race, and Age

The goal of the subgroup analysis is to assess the consistency of the treatment effect for Movantik to placebo across subgroups (identified by gender, age group, and race group) assessed by the primary endpoint (response to Movantik during Weeks 1 to 12) using ITT population. These subgroup efficacy results should be considered exploratory only and not intended to imply confirmatory hypothesis testing.

4.1.1 Study D3820C00004

For subgroup analysis, this reviewer applies Cochran-Mantel-Haenszel (CMH) test procedure stratified by the response to laxatives at baseline (LIR, LAR, LUR) to analyze data. This method was proposed by the applicant for the efficacy comparisons assessed by the primary endpoint.

Gender group (Male vs. Female)

Table 4.1.1.1 presents the results of treatment efficacy comparisons by gender group.

Table 4.1.1.1 (Reviewer's) Number of subjects in response to Movantik during Weeks 1 to 12 – Study D3820C00004

Females

Treatment Group	n	Number (%) of Patients Responding	Movantik versus Placebo[a]	
			% Difference	P-value
Placebo (P)	140	37 (26.4%)	NA	
Movantik 12.5 mg (M)	135	49 (36.3%)	9.9%	0.085
Movantik 25 mg (M)	118	53 (44.9%)	18.5%	0.0020*

Males

Treatment Group	n	Number (%) of Patients Responding	Movantik versus Placebo[a]	
			% Difference	P-value
Placebo (P)	74	26 (35.1%)	NA	
Movantik 12.5 mg (M)	78	38 (48.7%)	13.6%	0.088
Movantik 25 mg (M)	96	42 (43.8%)	8.7%	0.234

[a]: Analysis via Cochran Mantel-Haenszel test stratified by response to laxatives at baseline (LIR, LAR, LUR).
*: Significant at two-sided significance level of 0.025

Table 4.1.1.1 shows that for the female patients, the responder rate of subjects in the Movantik 25 mg group is significantly higher than that of placebo. However, the responder rate of Movantik 12.5 mg is numerically higher than that of placebo.

In addition, for male patients, the responder rates for both of Movantik 12.5 mg and 25 mg are numerically higher than that of placebo.

Race group (Caucasian vs. Non-Caucasian)

Table 4.1.1.2 presents the results of treatment efficacy comparisons by race group.

Table 4.1.1.2 (Reviewer's) Number of subjects in response to Movantik during Weeks 1 to 12 – Study D3820C00004

Caucasian

Treatment Group	n	Number (%) of Patients Responding	Movantik versus Placebo[a] % Difference	P-value
Placebo (P)	160	52 (32.5%)	NA	
Movantik 12.5 mg (M)	164	75 (45.7%)	13.2%	0.017*
Movantik 25 mg (M)	173	78 (45.1%)	12.6%	0.016*

Non-Caucasian

Treatment Group	n	Number (%) of Patients Responding	Movantik versus Placebo[a] % Difference	P-value
Placebo (P)	54	11 (20.4%)	NA	
Movantik 12.5 mg (M)	49	12 (24.5%)	4.1%	0.66
Movantik 25 mg (M)	41	17 (41.5%)	8.7%	0.024*

[a]: Analysis via Cochran Mantel-Haenszel test stratified by response to laxatives at baseline (LIR, LAR, LUR).
*: Significant at two-sided significance level of 0.025.

Table 4.1.1.2 shows that for the Caucasian patients, the responder rates of subjects in both of the Movantik 12.5 mg and 25 mg groups are significantly higher than that of placebo.

In addition, the responder rates of Movantik 25 mg for the Non-Caucasian patients also show a significantly higher effect than that of placebo.

Age group (age ≤ 65 versus age > 65)

Table 4.1.1.3 presents the results of treatment efficacy comparisons by Age group (age ≤ 65 versus age > 65).

Table 4.1.1.3 (Reviewer's) Number of subjects in response to Movantik during Weeks 1 to 12– Study D3820C00004

Age ≤ 65

Treatment Group	n	Number (%) of Patients Responding	Movantik versus Placebo[a] % Difference	P-value
Placebo (P)	195	57 (29.2%)	NA	
Movantik 12.5 mg (M)	194	75 (38.7%)	9.5%	0.055
Movantik 25 mg (M)	198	83 (41.9%)	12.7%	0.009*

Age > 65

Treatment Group	n	Number (%) of Patients Responding	Movantik versus Placebo[a] % Difference	P-value
Placebo (P)	19	6 (31.60%)	NA	
Movantik 12.5 mg (M)	19	12 (63.20%)	31.6%	0.073
Movantik 25 mg (M)	16	12 (75.0%)	43.4%	0.028

[a]: Analysis via Cochran Mantel-Haenszel test stratified by response to laxatives at baseline (LIR, LAR, LUR).
*: Significant at two-sided significance level of 0.025

Table 4.1.1.3 shows that for patients ≤ 65 years of age, the responder rate of subjects in the Movantik 25 mg group is significantly higher than that of placebo. However, the responder rate of Movantik 12.5 mg is numerically higher than that of placebo.

In addition, for patients over 65, the responder rates for both of Movantik 12.5 mg and 25 mg are numerically higher than that of placebo.

4.1.2 Study D3820C00005

Similar to Study D3820C00004, for subgroup analysis, this reviewer applies Cochran-Mantel-Haenszel (CMH) test procedure stratified by the response to laxatives at baseline (LIR, LAR, LUR) to analyze data.

Gender group (Male vs. Female)

Table 4.1.2.1 presents the results of treatment efficacy comparisons by gender group

Table 4.1.1.1 (Reviewer's) Number of subjects in response to Movantik during Weeks 1 to 12 – Study D3820C00005

Females

Treatment Group	n	Number (%) of Patients Responding	Movantik versus Placebo[a] % Difference	P-value
Placebo (P)	145	48 (33.1%)	NA	
Movantik 12.5 mg (M)	149	58 (38.9%)	5.8%	0.30
Movantik 25 mg (M)	147	58 (39.5%)	6.4%	0.28

Males

Treatment Group	n	Number (%) of Patients Responding	Movantik versus Placebo[a] % Difference	P-value
Placebo (P)	87	20 (23.0%)	NA	
Movantik 12.5 mg (M)	83	23 (27.7%)	4.7%	0.48
Movantik 25 mg (M)	85	34 (40.0%)	17.0%	0.016*

[a]: Analysis via Cochran Mantel-Haenszel test stratified by response to laxatives at baseline (LIR, LAR, LUR).
*: Significance at tow-sided significance level of 0.025.

Table 4.1.2.1 shows that for the male patients, the responder rate of subjects in the Movantik 25 mg group is significantly higher than that of placebo. However, the responder rate of Movantik 12.5 mg is numerically higher than that of placebo.

In addition, for female patients, the responder rates for both of Movantik 12.5 mg and 25 mg are numerically higher than that of placebo.

Race group (Caucasian vs. Non-Caucasian)

Table 4.1.2.2 (Reviewer's) Number of subjects in response to Movantik during Weeks 1 to 12– Study D3820C00005

Caucasian

Treatment Group	n	Number (%) of Patients Responding	Movantik versus Placebo[a] % Difference	P-value
Placebo (P)	183	54 (29.5%)	NA	
Movantik 12.5 mg (M)	187	68 (36.4%)	6.9%	0.15
Movantik 25 mg (M)	189	79 (41.8%)	12.3%	0.015*

Non-Caucasian

Treatment Group	n	Number (%) of Patients Responding	Movantik versus Placebo[a] % Difference	P-value
Placebo (P)	49	14 (28.6%)	NA	
Movantik 12.5 mg (M)	45	13 (28.9%)	0.3%	0.87
Movantik 25 mg (M)	43	13 (30.2%)	1.6%	0.88

[a]: Analysis via Cochran Mantel-Haenszel test stratified by response to laxatives at baseline (LIR, LAR, LUR).
*: Significant at two-sided significance level of 0.025

Table 4.1.2.2 shows that for the Caucasian patients, the responder rate of subjects in the Movantik 25 mg group is significantly higher than that of placebo. However, the responder rate of Movantik 12.5 mg is numerically higher than that of placebo.

In addition, for Non-Caucasian patients, the responder rates for both of Movantik 12.5 mg and 25 mg are numerically higher than that of placebo.

Age group (age ≤ 65 versus age > 65)

Table 4.1.2.3 presents the results of treatment efficacy comparisons by Age group (age ≤ 65 versus age > 65).

Table 4.1.2.3 (Reviewer's) Number of subject in response to Movantik during Weeks 1 to 12– Study D3820C00005

Age ≤ 65

Treatment Group	n	Number (%) of Patients Responding	Movantik versus Placebo[a] % Difference	P-value
Placebo (P)	207	59 (28.5%)	NA	
Movantik 12.5 mg (M)	207	69 (33.3%)	4.8%	0.3033
Movantik 25 mg (M)	202	81 (40.1%)	11.6%	0.0139*

Age > 65

Treatment Group	n	Number (%) of Patients Responding	Movantik versus Placebo[a] % Difference	P-value
Placebo (P)	25	9 (36.0%)	NA	
Movantik 12.5 mg (M)	25	12 (48.0%)	12.0%	0.339
Movantik 25 mg (M)	30	11 (36.7%)	0.7%	0.829

a: Analysis via Cochran Mantel-Haenszel test stratified by response to laxatives at baseline (LIR, LAR, LUR).
*: Significant at two-sided significance level of 0.025

Table 4.1.2.3 shows that for the patients ≤ 65 years of age, the responder rate of subjects in the Movantik 25 mg group is significantly higher than that of placebo. However, the responder rate of Movantik 12.5 mg is numerically higher than that of placebo.

In addition, for patients over 65, the responder rates for both of Movantik 12.5 mg and 25 mg are numerically higher than that of placebo.

4.2 Other Special / Subgroup Populations

For both studies, more than 90% of patients were enrolled in the U.S. and consequently no regional analyses (U.S vs. non-U.S.) were performed by this reviewer.

5.0 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The comments given below for the two studies (D3820C00004 and D3820C00005) are for Movantik 25 mg, based upon the applicant's analysis results from the NDA submission and the applicant's response document to the Agency IR letter. It is noted that for Study D3820C00005, the effect of Movantik 12.5 mg was not significantly better than that of placebo as assessed by the primary endpoint. Consequently Movantik 12.5 mg is not substantially supported by the submitted data and will not be further discussed.

Comments on Primary endpoint

Study D3820C00004

- The response rate assessed by the primary endpoint in Movantik 25 mg group was significantly higher than that of placebo (44.4% vs. 29.4%) using the applicant's ITT population, performed by the applicant from original NDA submission.

- Based upon the applicant's response to the IR and the re-analysis based on the All Randomized and FAS populations conducted by the sponsor, the response rate of Movantik 25 mg remained significantly higher than that of placebo.

- No center was deemed to have an abnormally large rate difference to dominate the superiority of Movantik 25 mg versus placebo.

- Therefore, it is the reviewer's conclusion that for Study D3820C00004, the superiority of Movantik 25 mg to placebo assessed by the primary endpoint is supported by the submitted data**.**

Study D3820C00005

- The response rate assessed by the primary endpoint in the Movantik 25 mg was significantly higher than that of placebo (39.7% vs 29.3%) using the applicant's ITT population.

- Based upon the applicant's response to the IR and the re-analysis based on the All Randomized and FAS populations conducted by the sponsor, the response rate of Movantik 25 mg remained significantly higher than that of placebo.

- The sizes of response rate differences of Movantik 25 mg versus placebo were evenly distributed across centers, and no center was deemed to have an abnormally large rate difference to dominate the superiority of Movantik 25 mg versus placebo.

- Therefore, it is the reviewer's conclusion that for Study D3820C00005, the superiority of Movantik 25 mg to placebo assessed by the primary endpoint is supported by the submitted data**.**

Comments on Key Secondary endpoints – Studies D3820C00004 and D3820C00005

- The efficacy comparisons of Movantik 25 mg versus placebo for the following three key secondary endpoints analyses assessed by the applicant showed positive results in favor of Movantik:
  - Response to study drug in the LIR subgroup during Weeks 1 to 12;
  - Time (in hours) to first post-dose laxation without use of rescue laxatives within 24 hours;
  - Mean number of days per week with at least one SBM during Weeks 1 to 12.
- Based upon the applicant's response document dated 01/10/2014, the efficacy comparisons of Movantik 25 mg versus placebo assessed by the three key secondary

endpoints using the All Randomized population also showed positive results in favor of Movantik.

5.2 Conclusions and Recommendations

Based upon this reviewer's efficacy comparisons on the primary endpoint and the applicant's analysis results on the primary endpoint and the key secondary endpoints, data submitted by the applicant support the efficacy of Movantik 25 mg.

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/s/

WEN JEN CHEN
06/19/2014

MICHAEL E WELCH
06/20/2014

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	IND 78,781/NDA 204-760
Drug Name:	NKTR-118 (Naloxegol)
Indication(s):	Two year Rat and Mouse Carcinogenicity Studies
Applicant:	Sponsor: AstraZeneca Wilmington, DE Testing Facility: (b) (4)
Documents Reviewed:	Electronic submission submitted on June 13, 2012 Electronic data submitted on January 30, 2013
Review Priority:	Standard
Biometrics Division:	Division of Biometrics - 6
Statistical Reviewer:	Mohammad Atiar Rahman, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Gastroenterology and Inborn Errors Products
Reviewing Pharmacologist:	Yuk-Chow Ng, Ph.D.
Project Manager:	Dewey Maureen
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of NKTR-118 (Naloxegol) when administered daily via oral gavage to rats and mice for at least 2 years. Results of this review have been discussed with the reviewing pharmacologist Dr. Ng.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Rat Study

Two separate experiments were conducted, one in male and one in female rats. In each of these two experiments there were three treated groups and one control group. Two hundred and forty Crl:CD(SD) rats of each sex were assigned randomly to the treated and control groups in equal size of 60 rats per group. The dose levels for treated groups were 40, 120, or 400 mg/kg/day. In this review these dose groups would be referred to as the low, medium, and high dose groups, respectively. The rats in the control group were treated with vehicle (water).

During the administration period all rats were observed twice daily for mortality, abnormalities, and signs of pain or distress. Detailed observations were done on all rats once during the predose phase, before dosing on Day 1, weekly thereafter, and on the day of scheduled sacrifice. The rats were palpated regularly for the appearance of masses during the clinical observations.

Body weights of all rats were measured during the predose phase, prior to dosing on Day 1, once weekly thereafter for Weeks 2 through 14, and then once every 4 weeks.

Since the survival of control rats reached 20 and 19 in males and females, respectively, based on the FDA executive CAC recommendations of 02 August 2010, dosing was terminated and all male rats were sacrificed on Week 93 and female rats were sacrificed on Week 94 of the dosing phase.

2.1. Sponsor's analyses

2.1.1. Survival analysis

The sponsor estimated the adjusted proportion of survival in each treated group in each sex using the Kaplan-Meier product-limit method, and displayed the related survival plots graphically. The data were analyzed for trend and heterogeneity using the Cox-Tarone binary regression method, and Gehan-Breslow nonparametric tests.

Sponsor's findings: The sponsor's count showed 20, 26, 31 and 35 male rat survivors; and 19, 18, 33 and 28 number of female rat survivors in control, low, medium, and high dose groups, respectively. The sponsor's analysis showed a statistically significant negative trend in mortality along with significantly lower mortality in medium and high dose groups compared to the control in male rats. In female rats the sponsor's analysis showed, although not as pronounced as in males, a significant negative trend and a significant decreased mortality in medium dose group compared to the control. In female rats the high dose group also showed a borderline nonsignificant decreased mortality compared to the control.

2.1.2. Tumor data analysis

The sponsor analyzed the neoplastic lesions if the incidence in at least one of the treated groups was increased or decreased by at least two occurrences over the control group. The incidental tumors were analyzed by linear logistic regression of tumor prevalence (Dinse and Lagakos, 1983). Fatal and palpable tumors were analyzed by the Cox-Tarone binary regression method using the death time or the first palpation time (as applicable) as a surrogate for the tumor onset time. In the case of a particular tumor type where the study pathologist assigned the tumor in question as the cause of death for a subset of the animals and not for the rest of the animals, the IARC-type (Peto et al., 1980) cause of death analysis was performed. Specifically, the subset of the tumors assigned as the cause of death by the study pathologist was analyzed by Cox-Tarone logistic regression and the subset, which was considered incidental by the pathologist, was analyzed by logistic regression of tumor prevalence. Tumor types in which the cause of death was undetermined were treated as incidental. The score statistics and their respective variances were then used to compute the combined evidence as described by Gart et al. (Gart et al., 1986). If there was only one tumor belonging to one of the two categories (fatal and incidental), it was combined with the other category for the purpose of statistical analyses. In addition, for incidental tumors only, in the cases where a lack of convergence for the asymptotic test of the logistic regression method was observed or when the tables were sparse (<5), the exact probability of significance was obtained by using LogXact-Turbo (LogXact, 2007).

For Peto analysis the dose levels of 0, 40, 120, and 400 were used as the scores in the analyses for Control, low, medium, and high dose groups, respectively. Continuity correction was used for all asymptotic tests.

Adjustment for multiple testing: For multiple testing adjustment the sponsor used the adjustment method suggested in the draft FDA guidance for the rodent carcinogenicity studies, i.e. the use of test levels of 0.005 and 0.025 in common (background incidence rate > 1%) and rare (background incidence < 1%) tumors, respectively for the dose response relationship test; and the use of test levels of 0.01 and 0.05 in common and rare tumors, respectively for the pairwise comparisons. However, in this study the sponsor used the test levels of 0.01 and 0.05 in common and rare tumor types, respectively for the pairwise comparison of high dose group with the control; and for the other intermediate, pairwise comparisons they used a test level of 0.05.

Sponsor's findings: The sponsor's analyses showed a statistically significant positive dose response relationship in interstitial (Leydig) cell adenomas in testis in male rats. The pairwise comparison showed a statistically significant increased incidence of interstitial (Leydig) cell hyperplasia in testis in the male rat medium dose group, and a borderline nonsignificant increased incidence of interstitial (Leydig) cell adenomas in the male rat high dose group compared to the control. In male rats, the combined incidence of interstitial cell hyperplasia and adenoma showed a nonsignificant positive trend with a nonsignificant increased incidence in high dose group, and a significant increased incidence in medium dose group compared to the control.

The sponsor concluded that, the increased incidence of interstitial (Leydig) cell hyperplasia and adenoma in male medium and high dose groups were possibly test article-related.

2.2. Reviewer's analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of rats in all treatment groups were estimated using the Kaplan-Meier product limit method. For control, low, medium, and high dose groups, the dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female rats, respectively. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

Reviewer's findings: This reviewer's analysis showed 20 (33%), 26 (43%), 31 (52%), and 35 (58%) number (percent) of survivors in male rats and 19 (32%), 18 (30%), 33 (55%), and 28 (47%) number (percent) of survivors in female rats in control, low, medium, and high dose groups, respectively. The tests showed statistically significant negative dose response relationship in mortality across control and treated groups in male rats. The pairwise comparisons showed statistically significant decreased mortality in the male rat high dose group and in the female rat medium dose group compared to their respective control.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of control group with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-K method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of s_h =1. An animal that dies at week w_h without a tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}} \right)^k < 1$. The adjusted group size is defined as Σs_h. As an interpretation, an animal with score s_h =1 can be considered as a whole animal while an animal with score $s_h <$ 1 can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male and female rats, respectively.

Multiple testing adjustment: For the adjustment of multiple testing this reviewer used the methodologies suggested in the FDA guidance for statistical aspects of the design, analysis, and interpretation of chronic rodent carcinogenicity studies of pharmaceuticals. For dose response relationship tests, the guidance suggests the use of test levels of α=0.005 for common tumors and α=0.025 for rare tumors for a submission with two species, and a significance level α=0.01 for common tumors and α=0.05 for rare tumors for a submission with one species in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. For multiple pairwise comparisons of treated group with control the guidance suggests the use of test levels of α=0.01 for

common tumors and α=0.05 for rare tumors, in order to keep the false-positive rate at the nominal level of approximately 10% for both submissions with two or one species.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Lin and Rahman (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 either for dose response relationship or pairwise comparisons of treated groups and control.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Control in Rats

							P_Value			
			Control	Low	Med	High	Dose	P_Value	P_Value	P_Value
Sex	Organ Name	Tumor Name	N=60	N=60	N=60	N=60	Resp	C vs. L	C vs. M	C vs. H
Male	Skin/Subcutis	B-Basal Cell Tumor	0	1	0	3	0.0448	0.5119	.	0.1568
	Testis	B-Interstitial Cell Adenoma	0	0	4	7	0.0016*	.	0.0733	0.0115*

Based on the criteria of adjustment for multiple testing discussed above, the incidences of B-interstitial cell adenoma in testis in male rats was considered to have statistically significant dose response relationship. In male rats, the pairwise comparison also showed statistically significant increased incidence of B-interstitial cell adenoma in testis in high dose group compared to the control.

3. Mouse Study

Two separate experiments were conducted, one in male and one in female mice. In each of these two experiments there were three treated groups and one control group. Two hundred and forty Crl:CD1(ICR) mice of each sex were assigned randomly to the treated and control groups in equal size of 60 mice per group. The initial dose levels for male treated groups were 25, 70 or 200 mg/kg/day, and that female mice were 40, 120 or 400 mg/kg/day. However, due to increased mortality of female mice in high dose group and to a lesser extent male mice in medium dose group, starting on Day 117 the dose levels of female mice medium and high dose groups were reduced to a dose level of 80 and 160 mg/kg/day, respectively, and starting on Day 118 the dose levels of male mice medium and high dose groups were reduced to a dose level of 50 and 100 mg/kg/day, respectively. In this review these dose groups were referred to as the low, medium, and high dose groups, respectively. Animals in the control group were treated with vehicle (water).

During the administration period all mice were observed twice daily for mortality, abnormalities, and signs of pain or distress. Detailed observations were done on all mice once during the predose phase, before dosing on Day 1, weekly thereafter, and on the day of scheduled sacrifice. The mice were palpated regularly for the appearance of masses during the clinical observations.

Body weights of all mice were measured during the predose phase, prior to dosing on Day 1, once weekly thereafter for Weeks 2 through 14, once for during Weeks 17, 18, 19, 20, 21, and 22; once every 4 weeks thereafter, and during Week 104 of the dosing phase.

3.1. Sponsor's analyses

3.1.1. Survival analysis

The sponsor used similar methodologies to analyze the mouse survival data as they used to analyze the rat survival data.

Sponsor's findings: The sponsor's count showed 32, 23, 23 and 23 number of male mouse survivors; and 23, 27, 31 and 22 number of female mouse survivors in control, low, medium, and high dose groups, respectively. The sponsor mentioned that there were early increased mortalities in the medium and/or high dose groups in both sexes. To reduce mortality in the remainder of the study, starting on Day 117 the dose levels of female mice medium and high dose groups were reduced to a dose level of 80 and 160 mg/kg/day, respectively, and starting on Day 118 the dose levels of male mice medium and high dose groups were reduced to a dose level of 50 and 100 mg/kg/day, respectively. The Executive CAC recommended these reductions in dose levels, in response to an inquiry from the sponsor (letter to sponsor dated June 9, 2009). After the reduction in dose levels, survival in the high-dose groups was comparable with the other groups.

3.1.2. Tumor data analysis

The sponsor used similar methodologies to analyze the mouse tumor data as they used to analyze the rat tumor data.

Adjustment for multiple testing: The sponsor used a similar procedure to adjust the multiple testing in the mouse tumor data analysis as they used to adjust the multiple testing in the rat data analysis.

Sponsor's findings: The sponsor's analyses did not show statistically significant increased incidence in any observed tumor type compared to the control in either sex. The sponsor concluded that the test article did not have any significant effect on the incidence of any tumor type in study mice.

3.2. Reviewer's analyses

Similar to the rat study, to verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses of mouse data. Data used in this reviewer's analyses were provided by the sponsor electronically.

For the analysis of both the survival data and the tumor data this reviewer used similar methodologies as he used for the analyses of the rat survival and tumor data.

3.2.1. Survival analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data of all treatment groups are given in Tables 4A and 4B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals for control, low, medium, and high dose groups are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed 32 (53%), 23 (38%), 23 (38%), and 23 (38%) number (percent) of survivor in male mice, and 23 (38%), 27 (45%), 31 (52%), and 22 (37%) number (percent) of

survivor in female mice in control, low, medium, and high dose groups, respectively. The tests did not show statistically significant dose response relationship in mortality across the treatment groups in either sex. The pairwise comparison also did not show statistically significant difference in mortality among treatment groups in either sex.

3.2.2. Tumor data analysis

The tumor rates and the p-values of the tested tumor types are given in Tables 6A and Table 6B in the appendix, for male and female mice respectively.

Reviewer's findings: Following tumor type showed p-values less than or equal to 0.05 either for dose response relationship or pairwise comparisons of treated groups with control.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups with Control in Mice

			Cont	Low	Med	High	P_Value			
Sex	Organ Name	Tumor Name	N=60	N=60	N=60	N=60	Dose Resp	C vs L	C vs M	C vs H
Male	Liver	M-Carcinoma, Hepatocellular	4	10	8	2	0.8506	0.0494	0.1064	0.8702

Based on the criteria of adjustment for multiple testing discussed in the rat data analysis section, the incidence of none of the observed tumor types was considered to have statistically significant dose response relationship in either sex of mice. The pairwise comparisons also did not show statistically significant increased incidence in any of the observed tumor types in any treated group compared to their respective controls in either sex.

On the suggestions of the Executive Carcinogenicity Assessment Committee (ECAC) members, this reviewer performed a re-analysis of mouse tumor data using the weighted average doses to account for the dose reductions in the medium and high dose groups. The re-analysis made very little changes in the p-values and the overall conclusion remained the same. The dose-response relationship p-value for male mouse hepatocellular carcinoma in the original analysis was 0.8506 (see the above table) and came out to be 0.8705 using the weighted average doses. The p-values for the pairwise comparisons remained the same.

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of NKTR-118 (Naloxegol) when administered daily via oral gavage to rats and mice for at least 2 years.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

Rat Study: Two separate experiments were conducted, one in male and one in female rats. In each of these two experiments there were three treated groups and one control group. Two hundred and forty Crl:CD(SD) rats of each sex were assigned randomly to the treated and control groups in equal size of 60 rats per group.

The dose levels for treated groups were 40, 120, or 400 mg/kg/day for both sexes. The rats in the control group were administered the vehicle control article.

During the administration period all rats were observed twice daily for mortality, abnormalities, and signs of pain or distress. Detailed observations were done on all rats once during the predose phase, before dosing on Day 1, weekly thereafter, and on the day of scheduled sacrifice. The rats were palpated regularly for the appearance of masses during the clinical observations. Body weights of all rats were measured during the predose phase, prior to dosing on Day 1, once weekly thereafter for Weeks 2 through 14, and then once every 4 weeks.

Since the survival of control rats reached 20 and 19 in males and females, respectively, based on the FDA executive CAC recommendations, dosing was terminated and all male rats were sacrificed on Week 93 and female rats on Week 94 of the dosing phase.

The tests showed statistically significant negative dose response relationship in mortality across control and treated groups in male rats. The pairwise comparisons showed statistically significant decreased mortality in the male rat high dose group and in the female rat medium dose group compared to their respective control. The tests showed statistically significant positive dose response relationship in the incidences of B-interstitial cell adenoma in testis in male rats. In male rats, the pairwise comparison also showed statistically significant increased incidence of B-interstitial cell adenoma in testis in high dose group compared to the control.

Mouse Study: Two separate experiments were conducted, one in male and one in female mice. In each of these two experiments there were three treated groups and one control group. Two hundred forty Crl:CD1(ICR) mice of each sex were assigned randomly to the treated and control groups in equal size of 60 mice per group. The initial dose levels for male treated groups were 25, 70 or 200 mg/kg/day, and that of female mice were 40, 120 or 400 mg/kg/day. However, due to increased mortality of female mice in high dose group and to a lesser extent male mice in medium dose group, starting on Day 117 the dose levels of female mice medium and high dose groups were reduced to a dose level of 80 and 160 mg/kg/day, respectively, and starting on Day 118 the dose levels of male mice medium and high dose groups were reduced to 50 and 100 mg/kg/day, respectively. The Executive CAC recommended these reductions in dose levels, in response to an inquiry from the sponsor (letter to sponsor dated June 9, 2009). Animals in the control group were treated with the vehicle control article..

Similar to rat study, during the administration period all mice were observed twice daily for mortality, abnormalities, and signs of pain or distress. Detailed observations were done on all mice once during the predose phase, before dosing on Day 1, weekly thereafter, and on the day of scheduled sacrifice. The mice were palpated regularly for the appearance of masses during the clinical observations. Body weights of all mice were measured during the predose phase, prior to dosing on Day 1, once weekly thereafter for Weeks 2 through 14, once during Weeks 17, 18, 19, 20, 21, and 22; once every 4 weeks; and during Week 104 of the dosing phase.

The tests did not show statistically significant dose response relationship in mortality across the treatment groups in either sex. The pairwise comparison also did not show statistically significant difference in mortality among treatment groups in either sex. The test did not show statistically significant dose response relationship in the incidence of any of the observed tumor types in either sex. The pairwise comparisons also did not show

statistically significant increased incidence in any of the observed tumor types in any treated group compared to their respective controls in either sex.

Mohammad Atiar Rahman, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D.
Team Leader, Biometrics-6

cc:
Archival NDA 204-760
Dr. Ng
Mr. Maureen
Dr. Tsong
Dr. Lin
Dr. Rahman
Ms. Patrician

5. Appendix

Table 1A: Intercurrent Mortality Rate
Male Rats

	0 mg|kg|day		40 mg|kg|day		120 mg|kg|day		400 mg|kg|day	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	9	15.00	6	10.00	4	6.67	3	5.00
53 - 78	15	40.00	15	35.00	13	28.33	13	26.67
79 - 92	16	66.67	13	56.67	12	48.33	9	41.67
Ter. Sac.	20	33.33	26	43.33	31	51.67	35	58.33
Total	N=60		N=60		N=60		N=60	

[#] Cum. %: Cumulative percentage except for Ter. Sac.

Table 1B: Intercurrent Mortality Rate
Female Rats

	0 mg|kg|day		40 mg|kg|day		120 mg|kg|day		400 mg|kg|day	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	3	5.00	5	8.33	4	6.67	6	10.00
53 - 78	22	41.67	18	38.33	12	26.67	13	31.67
79 - 93	16	68.33	19	70.00	11	45.00	13	53.33
Ter. Sac.	19	31.67	18	30.00	33	55.00	28	46.67
Total	N=60		N=60		N=60		N=60	

[#] Cum. %: Cumulative percentage except for Ter. Sac.

Table 2A: Intercurrent Mortality Comparison
Male Rats

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.0109
Homogeneity	Log-Rank	0.0407

Table 2B: Intercurrent Mortality Comparison
Female Rats

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.0998
Homogeneity	Log-Rank	0.0270

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Male Rats

Organ Name	Tumor Name	0 mg Control N=60	40 mg Low N=60	120 mg Med N=60	400 mg High N=60	P_Value Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Adrenal, Cortex	M-Carcinoma	0	0	1	0	0.5311	.	0.5287	.
Adrenal, Medull	B-Pheochromocytoma	3	4	3	1	0.9282	0.5270	0.7153	0.9585
	M-Malignant Pheochromocytoma	0	1	0	0	0.7684	0.5060	.	.
Body, Whole/Cav	M-Hemangiosarcoma	2	1	1	1	0.7220	0.8840	0.8994	0.9061
	M-Histiocytic Sarcoma	1	1	3	1	0.5886	0.7648	0.3529	0.7953
	M-Lymphosarcoma	0	2	1	2	0.2411	0.2650	0.5287	0.2936
	M-Malignant Hibernoma	0	0	1	0	0.5337	.	0.5341	.
Bone, Other	M-Osteosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Brain	B-Astrocytoma	0	1	0	1	0.3428	0.5119	.	0.5393
	B-Granular Cell Tumor	2	0	1	0	0.9115	1.0000	0.8994	1.0000
Cavity, Abdomin	B-Fibroma	0	1	0	0	0.7684	0.5060	.	.
Gl, Harderian	M-Fibrosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Gl, Mandib Sali	M-Fibrosarcoma	0	0	0	1	0.2712	.	.	0.5393
	M-Malignant Schwannoma	0	0	0	1	0.2712	.	.	0.5393
Jejunum	M-Carcinoma	0	0	1	0	0.5311	.	0.5287	.
Kidney	M-Carcinoma, Tubule Cell	0	1	0	0	0.7697	0.5119	.	.
Liver	B-Adenoma, Hepatocellular	0	0	2	1	0.2339	.	0.2767	0.5393
	Hepatocellular_Aen+Car	1	0	2	2	0.2074	1.0000	0.5436	0.5595
	M-Carcinoma, Hepatocellular	1	0	0	1	0.4700	1.0000	1.0000	0.7906
Lung	M-Squamous Cell Carcinoma	0	0	1	0	0.5337	.	0.5341	.
Muscle, Bi Fem	B-Fibroma	0	0	1	0	0.5311	.	0.5287	.
Muscle, Other	B-Fibroma	0	0	0	1	0.2712	.	.	0.5393
Pancreas	Acinar_cell_Aen+Car	0	1	3	0	0.7379	0.5119	0.1478	.
	B-Adenoma, Acinar Cell	0	1	2	0	0.6775	0.5119	0.2767	.
	B-Adenoma, Islet Cell	3	3	2	0	0.9826	0.6847	0.8536	1.0000
	Islet_cell_Aen+Car	3	4	2	2	0.8050	0.5400	0.8536	0.8648
	M-Carcinoma, Acinar Cell	0	0	1	0	0.5337	.	0.5341	.
	M-Carcinoma, Islet Cell	0	1	0	2	0.1273	0.5119	.	0.2880
Parathyroid	B-Adenoma	2	0	1	1	0.6238	1.0000	0.8994	0.9061
	M-Carcinoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Pituitary	B-Adenoma	39	33	37	31	0.9632	0.9362	0.8707	0.9891
	B-Adenoma, Pars Intermedia	0	0	1	0	0.5337	.	0.5341	.
Prostate	M-Carcinoma	0	0	1	0	0.5337	.	0.5341	.

(Table 3A Continued)

(Table 3A Continued)

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Male Rats

Organ Name	Tumor Name	0 mg Control N=60	40 mg Low N=60	120 mg Med N=60	400 mg High N=60	P_Value Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Skin/Subcutis	B-Adenoma, Sebaceous Gland	0	0	0	1	0.2712	.	.	0.5393
	B-Basal Cell Tumor	0	1	0	3	0.0448	0.5119	.	0.1568
	B-Fibroma	1	1	2	0	0.8258	0.7590	0.5517	1.0000
	B-Keratoacanthoma	2	1	3	3	0.3029	0.8840	0.5652	0.5848
	B-Lipoma	0	0	3	0	0.6320	.	0.1432	.
	B-Papilloma, Squamous Cell	1	2	0	0	0.9503	0.5181	1.0000	1.0000
	B-Pilomatricoma	0	2	3	1	0.5401	0.2650	0.1478	0.5393
	M-Fibrosarcoma	1	1	2	0	0.8229	0.7648	0.5436	1.0000
	M-Malignant Schwannoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	M-Neural Crest Tumor	0	0	0	1	0.2712	.	.	0.5393
Spinal Cord	B-Astrocytoma	0	0	0	1	0.2712	.	.	0.5393
Stomach, Nongl	B-Papilloma, Squamous Cell	0	0	1	0	0.5311	.	0.5287	.
Testis	B-Interstitial Cell Adenoma	0	0	4	7	0.0016*	.	0.0733	0.0115*
Thymus	B-Thymoma	0	0	1	0	0.5311	.	0.5287	.
	M-Malignant Thymoma	0	1	0	0	0.7697	0.5119	.	.
Thyroid	B-Adenoma, C-cell	7	7	10	5	0.8556	0.6144	0.3699	0.8797
	B-Adenoma, Follicular Cell	0	2	2	0	0.7778	0.2590	0.2767	.
	C-Cell_Aen+Car	8	7	11	7	0.7258	0.7145	0.3837	0.8002
	Follicular_cell_Aen+Car	2	4	3	1	0.8822	0.3610	0.5550	0.9061
	M-Carcinoma, C-Cell	1	0	1	2	0.1999	1.0000	0.7808	0.5595
	M-Carcinoma, Follicular Cell	2	2	1	1	0.7902	0.7100	0.8994	0.9061
Urinary Bladder	B-Fibroma	0	0	0	1	0.2712	.	.	0.5393
	B-Papilloma, Transitional Ce	1	0	0	0	1.0000	1.0000	1.0000	1.0000

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Rats

Organ Name	Tumor Name	0 mg Control N=60	40 mg Low N=60	120 mg Med N=60	400 mg High N=60	P_Value Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Adrenal, Medull	B-Ganglioneuroma	0	1	0	0	0.7619	0.4937	.	.
	B-Pheochromocytoma	0	0	2	0	0.5213	.	0.2832	.
Body, Whole/Cav	M-Hemangiosarcoma	0	1	0	0	0.7633	0.5000	.	.
	M-Histiocytic Sarcoma	1	0	1	0	0.7774	1.0000	0.7808	1.0000
	M-Lymphosarcoma	0	1	0	0	0.7633	0.5000	.	.
	M-Malignant Hibernoma	0	1	0	0	0.7619	0.4937	.	.
Bone, Other	B-Osteoma	0	0	0	1	0.2560	.	.	0.5181
Brain	B-Astrocytoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	B-Granular Cell Tumor	1	0	0	1	0.4541	1.0000	1.0000	0.7762
	M-Malignant Oligodendrogliom	0	1	0	0	0.7633	0.5000	.	.
Cervix	B-Granular Cell Tumor	0	0	1	1	0.2060	.	0.5402	0.5181
	B-Polyp, Endometrial Stromal	0	0	0	1	0.2560	.	.	0.5181
	M-Leiomyosarcoma	0	0	0	1	0.2604	.	.	0.5238
	M-Malignant Schwannoma	1	0	0	1	0.4475	1.0000	1.0000	0.7708
Duodenum	M-Carcinoma	0	0	0	1	0.2604	.	.	0.5238
Gl, Zymbal's	M-Carcinoma	0	1	0	0	0.7619	0.4937	.	.
Heart	M-Endocardial Schwannoma	0	0	1	0	0.5298	.	0.5349	.
Jejunum	B-Leiomyoma	0	0	1	0	0.5298	.	0.5349	.
Kidney	B-Lipoma	1	0	1	0	0.7774	1.0000	0.7808	1.0000
	M-Carcinoma, Tubule Cell	0	0	0	1	0.2604	.	.	0.5238
Liver	B-Adenoma, Hepatocellular	2	1	1	1	0.7037	0.8703	0.8994	0.8921
	Hepatocellular_Aen+Car	3	1	1	1	0.8117	0.9360	0.9545	0.9500
	M-Carcinoma, Hepatocellular	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Mammary, Female	B-Adenoma	0	0	1	1	0.2054	.	0.5349	0.5181
	B-Fibroadenoma	15	13	19	18	0.2483	0.7309	0.3734	0.3918
	M-Carcinoma	19	10	12	9	0.9675	0.9803	0.9799	0.9952
	M-Fibrosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Muscle, Other	M-Malignant Schwannoma	0	0	1	0	0.5325	.	0.5402	.
Omentum	M-Malignant Schwannoma	0	0	0	1	0.2560	.	.	0.5181
Ovary	B-Sertoli Cell Tumor	0	0	1	0	0.5298	.	0.5349	.
Pancreas	B-Adenoma, Islet Cell	0	1	3	3	0.0907	0.4937	0.1483	0.1390
	Islet_cell_Aen+Car	1	4	3	4	0.2430	0.1642	0.3529	0.2028
	M-Carcinoma, Islet Cell	1	3	0	1	0.7368	0.2889	1.0000	0.7648
Parathyroid	B-Adenoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000

(Table 3B Continued)

(Table 3B Continued)

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Rats

Organ Name	Tumor Name	0 mg Control N=60	40 mg Low N=60	120 mg Med N=60	400 mg High N=60	P_Value Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Pituitary	B-Adenoma	53	49	46	45	0.8987	0.8875	0.9066	0.9630
	M-Carcinoma	1	1	1	0	0.8523	0.7532	0.7915	1.0000
Skin/Subcutis	B-Fibroma	0	0	0	1	0.2560	.	.	0.5181
	B-Keratoacanthoma	0	2	0	0	0.8332	0.2405	.	.
	B-Lipoma	1	0	0	1	0.4453	1.0000	1.0000	0.7648
	M-Fibrosarcoma	0	1	0	0	0.7619	0.4937	.	.
Thymus	B-Thymoma	0	1	0	0	0.7633	0.5000	.	.
	M-Malignant Thymoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Thyroid	B-Adenoma, C-cell	5	4	8	7	0.2657	0.7465	0.3869	0.4301
	B-Adenoma, Follicular Cell	2	0	0	0	1.0000	1.0000	1.0000	1.0000
	C-Cell_Aen+Car	5	4	8	7	0.2657	0.7465	0.3869	0.4301
	Follicular_cell_Aen+Car	2	1	0	0	0.9865	0.8703	1.0000	1.0000
	M-Carcinoma, Follicular Cell	0	1	0	0	0.7619	0.4937	.	.
Urinary Bladder	B-Papilloma, Transitional Ce	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Uterus	B-Polyp, Endometrial Stromal	3	1	2	4	0.1971	0.9327	0.8528	0.5264
	M-Carcinoma	0	0	0	1	0.2560	.	.	0.5181
Vagina	B-Granular Cell Tumor	0	0	2	2	0.0812	.	0.2832	0.2654

Table 4A: Intercurrent Mortality Rate in Male Mice

Week	0 mg|kg|day No. of Death	Cum. %	25 mg|kg|day No. of Death	Cum. %	70/50 mg|kg|day No. of Death	Cum. %	200/100 mg|kg|day No. of Death	Cum. %
0 - 52	4	6.67	7	11.67	11	18.33	11	18.33
53 - 78	10	23.33	12	31.67	8	31.67	5	26.67
79 - 91	7	35.00	7	43.33	10	48.33	5	35.00
92 - 104	7	46.67	11	61.67	8	61.67	16	61.67
Ter. Sac.	32	53.33	23	38.33	23	38.33	23	38.33
Total	N=60		N=60		N=60		N=60	

[#] **Cum. %: Cumulative percentage except for Ter. Sac.**

Table 4B: Intercurrent Mortality Rate Female Mice

Week	0 mg|kg|day No. of Death	Cum. %	40 mg|kg|day No. of Death	Cum. %	120/80 mg|kg|day No. of Death	Cum. %	400/160 mg|kg|day No. of Death	Cum. %
0 - 52	7	11.67	10	16.67	3	5.00	18	30.00
53 - 78	9	26.67	6	26.67	10	21.67	5	38.33
79 - 91	11	45.00	7	38.33	7	33.33	6	48.33
92 - 104	10	61.67	10	55.00	9	48.33	9	63.33
Ter. Sac.	23	38.33	27	45.00	31	51.67	22	36.67
Total	N=60		N=60		N=60		N=60	

[#] **Cum. %: Cumulative percentage except for Ter. Sac.**

Table 5A: Intercurrent Mortality Comparison Male Mice

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.2222
Homogeneity	Log-Rank	0.2705

Table 5B: Intercurrent Mortality Comparison Female Mice

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.3867
Homogeneity	Log-Rank	0.1297

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice

Organ Name	Tumor Name	0mg Control N=60	25mg Low N=60	70/50mg Med N=60	200/100mg High N=60	P_Value Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Adipose Tissue	B-Lipoma	0	2	0	0	0.7899	0.2238	.	.
Adrenal, Cortex	B-Adenoma, Cortical Cells	4	1	1	2	0.7757	0.9648	0.9602	0.8821
	B-Adenoma, Subcapsular Cell	4	4	0	1	0.9682	0.5884	1.0000	0.9648
Body, Whole/Cav	B-Hemangioma	0	0	1	0	0.4783	.	0.4568	.
	M-Hemangiosarcoma	2	2	4	0	0.8339	0.6461	0.2721	1.0000
	M-Histiocytic Sarcoma	0	0	0	1	0.2484	.	.	0.4762
	M-Lymphosarcoma	11	10	6	10	0.5293	0.5823	0.8761	0.5582
Bone, Other	M-Osteosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Gallbladder	B-Adenoma	1	0	0	2	0.1918	1.0000	1.0000	0.4639
Gl, Harderian	B-Adenoma	7	6	10	8	0.2750	0.6451	0.1936	0.4225
	M-Carcinoma	0	1	1	0	0.6045	0.4762	0.4634	.
Kidney	B-Adenoma, Tubule Cell	0	0	1	0	0.4783	.	0.4568	.
Liver	B-Adenoma, Hepatocellular	7	8	8	3	0.8797	0.4022	0.3609	0.9289
	Hepatocellular_Aen+Car	10	16	15	5	0.9098	0.0868	0.0766	0.9228
	M-Carcinoma, Hepatocellular	4	10	8	2	0.8506	0.0494	0.1064	0.8702
Lung	B-Adenoma, Bronchiolar-Alveo	15	9	6	9	0.8661	0.9015	0.9770	0.9015
	Bronchiolar-aveolar_Aen+Car	18	17	12	16	0.5652	0.6047	0.8503	0.5936
	M-Carcinoma, Bronchiolar-Alv	5	8	6	7	0.3301	0.2455	0.3979	0.3300
Pituitary	B-Adenoma	2	1	2	0	0.8825	0.8563	0.6146	1.0000
Skin/Subcutis	B-Papilloma, Squamous Cell	0	0	0	1	0.2484	.	.	0.4762
	M-Lymphangiosarcoma	0	1	0	0	0.7267	0.4762	.	.
	M-Neurofibrosarcoma	0	1	0	0	0.7267	0.4762	.	.
Testis	B-Interstitial Cell Tumor	4	1	4	5	0.2039	0.9648	0.5419	0.4544
	B-Sertoli Cell Tumor	0	1	0	0	0.7267	0.4762	.	.
	M-Interstitial Cell Tumor	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	M-Malignant Sertoli Cell Tum	1	1	0	0	0.9241	0.7227	1.0000	1.0000
Thyroid	B-Adenoma, Follicular Cell	2	0	0	0	1.0000	1.0000	1.0000	1.0000

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Mice

Organ Name	Tumor Name	0mg Control N=60	40mg Low N=60	120/80mg Med N=60	400/160mg High N=60	P_Value Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Adrenal, Cortex	B-Adenoma, Subcapsular Cell	1	1	2	0	0.7654	0.7651	0.5446	1.0000
Body, Whole/Cav	B-Hemangioma	1	4	4	3	0.2447	0.2111	0.2346	0.2685
	M-Hemangiosarcoma	4	2	3	3	0.5287	0.9149	0.8369	0.7120
	M-Histiocytic Sarcoma	5	2	0	2	0.9066	0.9491	1.0000	0.9117
	M-Lymphosarcoma	23	24	27	10	0.9850	0.5843	0.5492	0.9912
Brain	B-Meningioma	0	1	0	0	0.7531	0.5181	.	.
Cecum	M-Leiomyosarcoma	0	0	0	1	0.2112	.	.	0.4595
Cervix	B-Fibroma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	B-Leiomyoma	0	0	1	1	0.1623	.	0.5294	0.4595
	B-Vaginal Polyp	0	1	0	0	0.7516	0.5122	.	.
	M-Leiomyosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	M-Sarcoma, Endometrial Strom	0	0	0	1	0.2112	.	.	0.4595
Gl, Harderian	B-Adenoma	5	2	4	4	0.4428	0.9491	0.8123	0.6567
	M-Carcinoma	0	2	1	1	0.3691	0.2654	0.5349	0.4595
Kidney	B-Adenoma, Tubule Cell	1	0	0	1	0.4526	1.0000	1.0000	0.7045
Liver	B-Adenoma, Hepatocellular	2	0	0	1	0.7081	1.0000	1.0000	0.8476
	Hepatocellular_Aen+Car	2	0	2	1	0.5872	1.0000	0.7353	0.8476
	M-Carcinoma, Hepatocellular	0	0	2	0	0.4557	.	0.2773	.
Lung	B-Adenoma, Bronchiolar-Alveo	5	8	10	5	0.4499	0.3066	0.2142	0.5227
	Bronchiolar-aveolar_Aen+Car	7	11	12	7	0.4684	0.2297	0.2590	0.4856
	M-Carcinoma, Bronchiolar-Alv	3	3	2	2	0.6738	0.6737	0.8536	0.7571
Mammary, Female	B-Adenoma	1	0	0	1	0.4557	1.0000	1.0000	0.7112
	M-Adenoacanthoma	0	1	0	0	0.7516	0.5122	.	.
	M-Carcinoma	0	0	2	0	0.4561	.	0.2832	.
	M-Sarcoma	0	0	0	1	0.2112	.	.	0.4595
Ovary	B-Adenoma	1	0	2	2	0.1588	1.0000	0.5529	0.4385
	B-Granulosa/Theca Cell Tumor	1	0	1	0	0.8090	1.0000	0.7815	1.0000
	M-Malignant Granulosa/Theca	1	1	1	0	0.8357	0.7651	0.7815	1.0000
Pancreas	B-Adenoma, Islet Cell	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Pituitary	B-Adenoma	1	3	2	2	0.3738	0.3265	0.5529	0.4385
Skin/Subcutis	M-Fibrosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Stomach, Nongl	M-Carcinoma, Squamous Cell	0	1	0	0	0.7516	0.5122	.	.
Thyroid	B-Adenoma, Follicular Cell	1	1	1	1	0.5029	0.7651	0.7815	0.7112
Uterus	B-Fibroma	1	0	0	0	1.0000	1.0000	1.0000	1.0000

(Table 6B Continued)

(Table 6B Continued)

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Mice

Organ Name	Tumor Name	0mg Control N=60	40mg Low N=60	120/80mg Med N=60	400/160mg High N=60	P_Value Dose Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Uterus	B-Leiomyoma	0	0	2	0	0.4557	.	0.2773	.
	B-Polyp, Endometrial Stromal	5	4	6	3	0.6554	0.7708	0.5972	0.7995
	M-Carcinoma	1	0	1	1	0.4099	1.0000	0.7815	0.7112
	M-Leiomyosarcoma	2	0	0	1	0.7081	1.0000	1.0000	0.8476
	M-Sarcoma, Endometrial Strom	1	0	1	0	0.8051	1.0000	0.7756	1.0000
Vagina	B-Squamous Cell Papilloma	0	1	0	0	0.7516	0.5122	.	.
	B-Vaginal Polyp	1	3	1	1	0.6546	0.3265	0.7815	0.7112
	M-Sarcoma	0	0	1	0	0.4938	.	0.5349	.

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

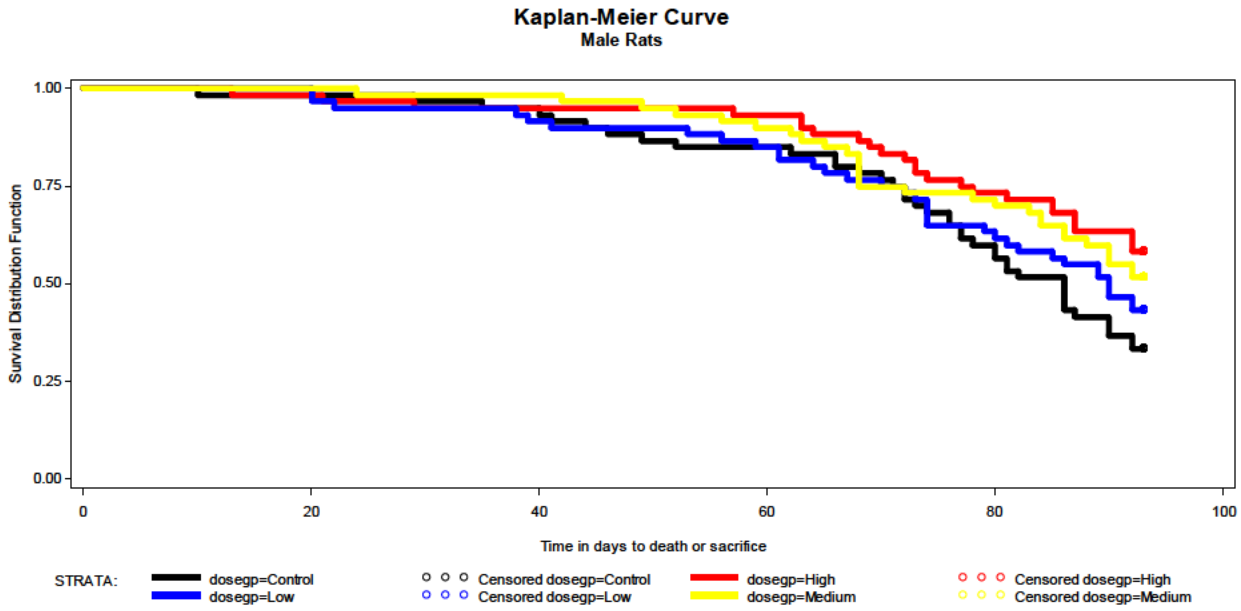


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

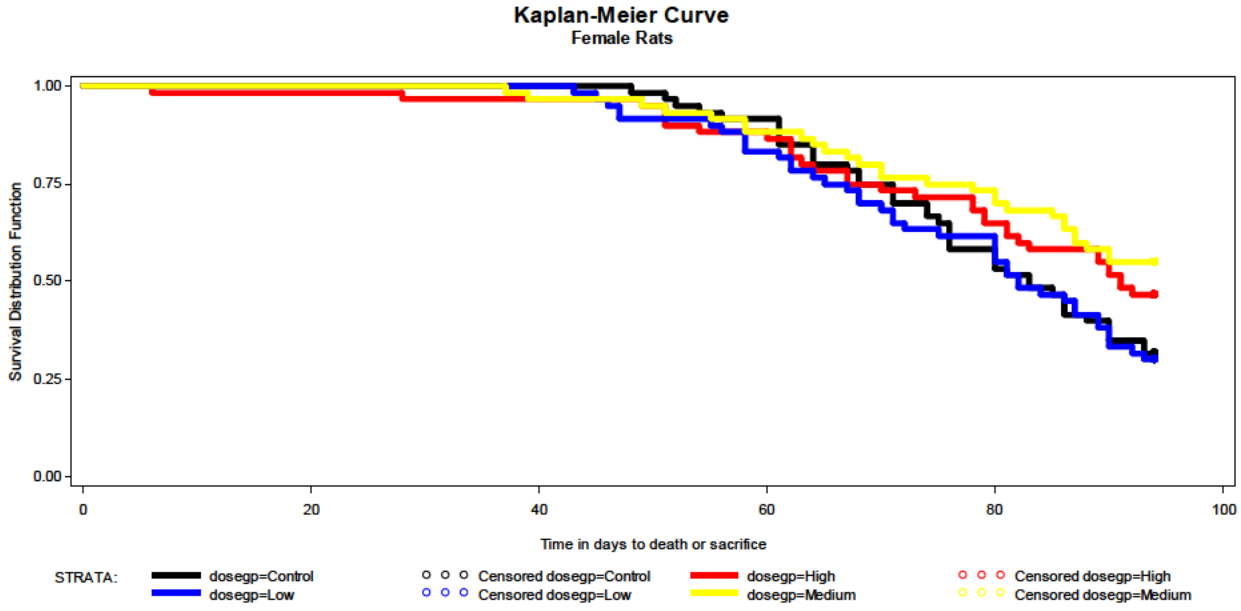


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

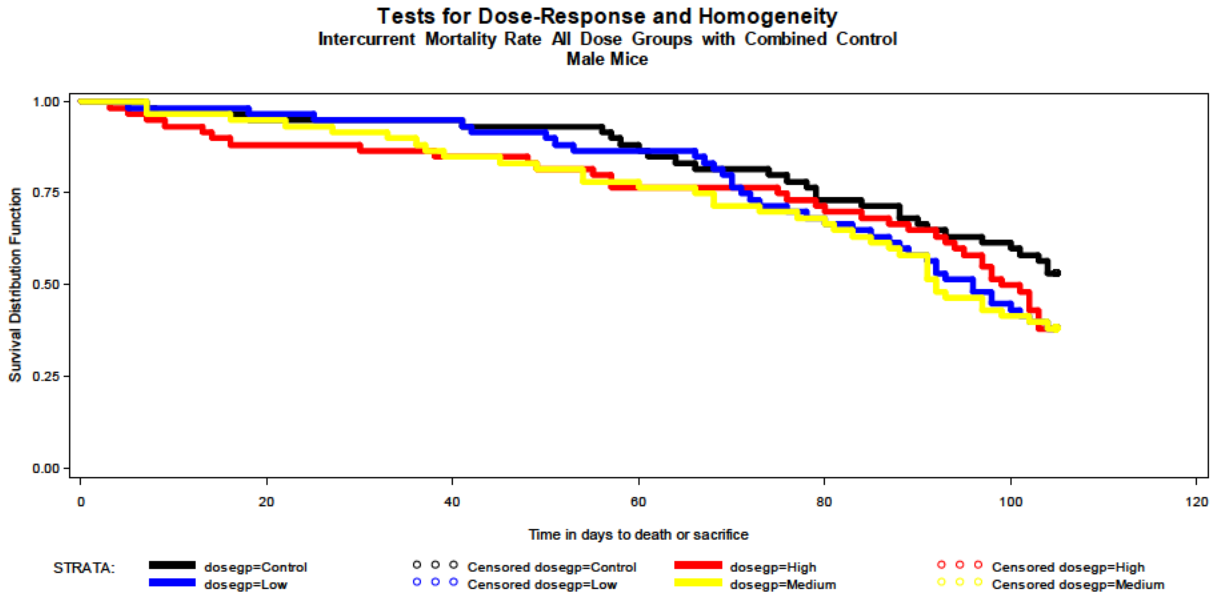
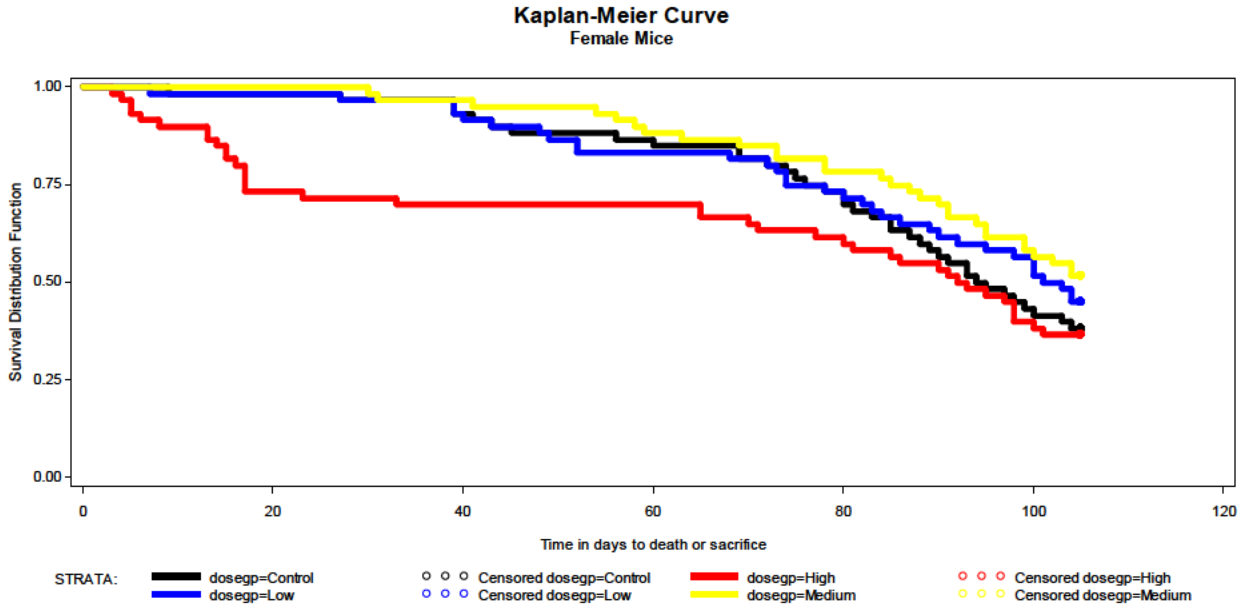


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



6. References

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/s/

MOHAMMAD A RAHMAN
02/07/2014

KARL K LIN
02/11/2014
Concur with review

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 204-760 **Applicant:** AstraZeneca Phamaceuticals LP **Stamp Date:** 09/16/2013

Drug Name: Movantik (Naloxegol Oxalate) tablets **NDA Type:** Standard **Indication:** Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain

On **initial** overview of the NDA application for RTF:

	Content Parameter for RTF	Yes	No	NA	Comments
1	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Efficacy was investigated for gender, racial, and geriatric subgroups investigated.	X			Sample size might be inadequate for gender and racial subgroup analyses
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION IS FILEABLE ? Yes

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	No interim analyses were planned
Appropriate references for novel statistical methodology (if present) are included.	X			Two articles regarding multiplicity adjustment methods were provided by

				the sponsor
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Background

This NDA submission mainly contained two phase 3 trials (Studies D3820C00004 and D3820C00005) to support the use of Naloxegol for treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

Review Issues/Concerns

This reviewer may request additional data from the sponsor to aid the sensitivity analyses. In addition, a guidance to locate the SAS programs for the primary and secondary endpoints analyses may be requested.

For the two pivotal studies, although two doses (NKTR-118 12.5 mg and 25 mg) were studied, only the high dose reportedly showed statistically significant treatment effect comparing to the placebo on the primary and three key secondary endpoints. The sponsor is only seeking approval for the high dose. It will be a review issue to determine whether or not the efficacy of the high dose is supported by the data within this submission for the proposed indication.

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/s/

WEN JEN CHEN
11/06/2013

FREDA COONER
11/06/2013