Janssen Research & Development

Department of Global Clinical Pharmacology

Population Pharmacokinetics and Pharmacodynamics Analysis Plan

JNJ-67953964 (Aticaprant)

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1. INTRODUCTION

JNJ-67953964, previously known as Cerecor (CERC)-501 and LY2456302, is a small molecule, high-affinity, selective kappa opioid receptor (KOR) antagonist. JNJ-67953964 is orally bioavailable and suitable for once-daily (QD) administration.

KORs and their native ligand dynorphin are localized in areas of the brain that effect reward and stress and may play a key role in mood, stress, and addictive disorders. Chronic stress, substance abuse, and acute withdrawal lead to increased dynorphin expression, activating KORs and subsequent downstream signaling pathways to inhibit mesolimbic dopamine surge, contributing to negative affective states. The behavioral pharmacology of KOR antagonism has been tested in animal models of anhedonia, depression, and anxiety and found to have meaningful effects that may translate to therapeutic benefit in humans. KOR antagonists may be effective for the treatment of patients with mood disorders, perhaps by modulating the negative affective state associated with stress response.

Only about 50% of patients with major depressive disorder (MDD) show a meaningful response (>50% improvement to a first line antidepressant treatment), leaving many patients with substantial persistent impairment. Therapeutic strategies such as switching antidepressants and using adjuvant drug treatments can improve response, however almost 40% of patients remain symptomatic and fail to achieve full remission. Recently, Alkermes (ALKS) 5461, a combination of buprenorphine, which is a partial μ-opioid receptor agonist and KOR antagonist, and samidorphan, a potent μ-opioid receptor antagonist, has been tested in Phase 2 trials in subjects with MDD who have had only a partial response to treatment with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI). Adjunctive treatment with ALKS 5461 was associated with greater symptom reduction compared to placebo, suggesting that a KOR antagonist could provide a meaningful clinical benefit for patients being treated for MDD.

A Phase 2a investigator-initiated study (FAST-MAS), evaluated whether JNJ-67953964 engages neural circuitry related to hedonic response to a monetary reward task. Subjects with mood and/or anxiety disorders and anhedonia were randomized to 8 weeks of double-blind treatment with 10 mg JNJ 67953964 (N=43) or placebo (N=44). The primary outcome measure was the functional MRI (fMRI) response to a Monetary Incentive Delay Task conducted at baseline and after 8 weeks of treatment. The activation of brain regions implicated with reward were evaluated with mixed-model analysis of variance (ANOVA) in 68 subjects. Mixed-model analyses revealed a significant Group×Time interaction in reward gain anticipation ($p=0.019$) (a priori primary outcome) and loss anticipation ($p<0.001$), consistent with relatively greater ventral striatal activation during anticipation of both gain and loss in the JNJ 67953964 group post treatment. The results of this study establish that KOR antagonism has the hypothesized effect on neural function, thereby establishing proof of concept that engaging this target can modulate neuronal circuits relevant to reward and hedonic response.

In the study 67953964MDD2001 the efficacy of JNJ-67953964 compared to placebo is evaluated when administered as adjunctive treatment in subjects with MDD partially responsive to

SSRI/SNRI treatment in terms of reduction of symptoms of depression. Depression in this study is primarily assessed by the change from baseline on the Montgomery Asberg Depression Rating Scale (MADRS) in non-responders during the placebo lead-in period.

The MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment.[8] The scale consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability.

The SHAPS[10,15] is a self-reported 14-item, instrument, developed for the assessment of hedonic capacity. It has excellent internal consistency, with construct validity, and is unidimensional in assessing hedonic capacity among adult patients with MDD. Subjects score whether they experience pleasure in performing a list of activities or experiences. Subjects can rate the answers a "definitely/strongly agree", "agree", "disagree" or "strongly disagree". Answers will be rated according to Franken[5]: "Definitely agree" will be rated 1, "Agree" will be rated 2, "Disagree" will be rated 3, and "Definitely disagree" will be rated 4. So, the score of the scale will range from 14 to 56. The mean score in a population of patients hospitalized for treatment of depression was 34.4[5].

2. OBJECTIVES

The primary objectives of the population pharmacokinetic (PK) and pharmacodynamic (PD) analysis are as follows:

- To characterize the pharmacokinetics of 10 mg qd JNJ-67953964 after oral administration, including
  - an exploratory analysis to determine if any relevant covariate could explain the variability in exposure of JNJ-67953964;
  - derivation of individual exposure parameters for JNJ-67953964 (i.e. area under the plasma concentration-time profile of JNJ-67953964 over 24 hours, $AUC_{0\text{-}24h}$ maximum plasma concentration, C_{max}, and pre-dose plasma concentrations, C_{0h}). Exposure metrics will be derived from the popPK model on the study days with MADRS and SHAPS assessments;
- To explore the relationship of JNJ-67953964 exposure with efficacy using the change from baseline in Montgomery-Asberg Depression Scale (MADRS) total score and change from baseline in Snaith-Hamilton Pleasure Scale (SHAPS);
- To explore potential relationship between JNJ-67953964 exposure and pre-defined safety parameters. AEs of special interest may include pruritus and gastrointestinal (GI) complaints.

3. DATA

The database for population PK analysis and a dataset for the ER analysis will be created by Janssen R&D and/or the external data management provider SGS or Quintiles PK Office based on the clinical databases and according to Janssen R&D specifications. For the three Phase 1 trials, databases are prepared per trial, and merged subsequently with the PK dataset prepared for MDD2001 to establish a pooled PK dataset. The dataset preparation step for the pooled PK dataset should be reviewed according to the internal Janssen Job Aid for Data Flow or Internal Data Preparation. If necessary, minor data management to assemble a suitable NONMEM dataset may be performed. Any modifications to the PK or ER dataset, as well as the merge of the derived individual exposure metrics to the ER dataset will be described in the final report, and the R script used for modification and merging of the data set will be included as an appendix to the final report.

3.1. Description of the Available Data

General information about the studies to be included in the Population PK analysis is summarized Table 1, and for Exposure-Response analysis in Table 2. Further studies may be added as appropriate.

All plasma PK samples with available date and time of both blood collection as well as preceding JNJ-67953964 dose administration will be used for the analysis. Subjects who have not received at least 1 dose of study drug (either JNJ-67953964 or placebo) will not be included in the analysis dataset. PK, MADRS and SHAPS data from subjects with missing dosing information and/or with incomplete dosing may only be included up to the time point of first occurrence of the missing dosing information/incomplete dosing. In case of miss-dosing (e.g. subject took one 5-mg capsule instead of two) the records will be handled as such and not be excluded. Any JNJ-67953964 concentrations before the administration of the first dose of JNJ-67953964 will lead to the exclusion of the subject from the analysis (ie, included in the dataset but commented out).

Baseline is defined as the last observation before the first dose administration of the treatment period (i.e. Treatment baseline) for MADRS, SHAPS and safety parameters. Data from screening and the lead-in period will not be included in the analysis. The primary analysis will be performed on data from the treatment period only.

No records will be deleted from the datasets: records that, for any reason, are excluded from the analysis will be commented out (i.e., including the letter “C” at the beginning of each excluded record or using a designated flag column).

Table 1: Overview of Trials to be Included in the Population PK Analysis

Study No.	Study Title & Design	Brief Description of PK Data
67953964MDD2001	Title: A Phase 2a Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Multi-center Study Investigating the Efficacy, Safety, Tolerability and Pharmacokinetics of JNJ-67953964 in Subjects with Major Depressive Disorder. Design: The treatment phase of the trial will consist of 3 periods. A placebo lead-in period of concealed duration, after which subjects will enter the double-blind treatment period when they will be randomly assigned to 10 mg JNJ-67953964 q.d. or continue placebo in a 1:1 ratio for 6 weeks. Subjects who complete the treatment period, will then enter the withdrawal period and be treated with placebo for the remaining time of the treatment phase of the study.	No. of subjects with PK data available/total no. in study: 71/142 (Planned) PK samples are collected for plasma concentrations of JNJ-67953964 before and 2 hours after dosing on Day 22 (Day 1 Treatment Period), 29 (Trt Week 1), 43 (Trt Week 3) and 64 (Trt Week 6).
LAFA	Single Ascending Dose, Fasted Cohort 1: 4, 25, 60 mg + placebo (15 subjects) Cohort 2: 2 and 10 mg + placebo (9 subjects) Cohort 3: 4, 10, 25, 60 mg + Fentanyl (10 subjects)	No. of subjects with PK data available/total : 30/31 PK samples are collected at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, and 96 h
LAFB	Multiple Ascending Dose, Fasted Cohort 4: 2 mg q.d. (9 subjects) Cohort 5: 35 mg q.d. (9 subjects) Cohort 6: 10 mg q.d. + ethanol (10 subjects)	No. of subjects with PK data available/total : 28/37 PK samples are collected at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96.0, 120, 144, 168, 192, 216, 264 h
LAFC	Receptor Occupancy (PET) 0.5 mg (1), 2 mg (4), 4 mg (2), 10 mg (4), 25 mg (1 subject)	No. of subjects with PK data available/total : 12/12 PK sample are collected at 0.5, 1.0, 2.5, 4, 6, 8, 12, 22.5 h

Table 2: Overview of Trials to be Included in the Exposure-Response Analysis

Study No.	Study Title & Design	Brief Description of Exposure and Response Data
67953964MDD2001	Title: A Phase 2a Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Multi-center Study Investigating the Efficacy, Safety, Tolerability and Pharmacokinetics of JNJ-67953964 in Subjects with Major Depressive Disorder. Design: The treatment phase of the trial will consist of 3 periods. A placebo lead-in period of concealed duration, after which subjects will enter the double-blind treatment period when they will be randomly assigned to 10 mg JNJ-67953964 q.d. or continue placebo in a 1:1 ratio for 6 weeks. Subjects who complete the treatment period, will then enter the withdrawal period and be treated with placebo for the remaining time of the treatment phase of the study.	No. of subjects with Exposure data available/total no. in study : 71/142 (Planned) Exposure metrics derived from popPK on Day 22, 29, 43, 50, 57 (Trt Week 0, 1, 3, 4, 5 and 6) and 78 (EOS). No. of subjects with MADRS and SHAPS data available/total no. in study : 142/142 (Planned) MADRS and SHAPS assessment at Screening (Week -5 to 0) and on Day 1, 8, 15 (Lead-in Week 0, 1, 2), 22, 29, 43, 50, 57 (Trt Week 0, 1, 3, 4, 5 and 6) and Day 78 (EOS). Safety assessments: All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety.

3.2. Handling Missing Data

3.2.1. Missing Concentration Values

Missing plasma concentration values will be treated as missing and will not be replaced with estimated (imputed) values. In the event of duplicate concentrations (samples from the same subject taken at the same time), all duplicated original values will be retained in the dataset but commented out and an additional data record will be included with the median concentration of the excluded duplicated samples.

3.2.2. Missing MADRS or SHAPS scores

Missing on-treatment MADRS total or SHAPS scores will be treated as missing and will not be replaced with estimated (imputed) values. If the baseline MADRS or SHAPS is missing in the source data, its value in the analysis dataset will be populated with median of the treatment baseline for the corresponding lead-in response group (placebo-responder or placebo-non-responder.

3.2.3. Missing Date and Time Records

Concentration records with the following missing information will generally be excluded from the analysis: 1) recorded sampling date and time; 2) dosing information immediately prior to the sample collection time; 3) irresolvable discrepancy between recorded sampling date/time or dosing date/time.

MADRS or SHAPS total score values with the following missing information will generally be excluded from the analysis: 1) recorded assessment date; 2) dosing information on the assessment day; 3) irresolvable discrepancy between recorded MADRS or SHAPS assessment date or dosing date.

3.2.4. Missing Covariate Values

If only limited covariates from a subject are missing, data can be imputed with one of the following methods:

- For a given covariate, if no more than 10% of all subjects in the analysis population have missing values, then these missing values will be imputed with the median or mean (for continuous covariates) or mode (for categorical covariates) of the non-missing values from appropriate populations (studies), or
- If predictors are correlated, then the missing data will be imputed based on the model that describes the relationship of each predictor to all other predictors.

In cases where the baseline value of a covariate is missing:

- If the covariate value was recorded for the individual at an earlier assessment period, that earlier value will be carried forward.
- If the covariate was not recorded for the individual at an earlier assessment period, but is available from a later assessment, that later value will be carried backward wherever appropriate.

For categorical covariates values which are missing, a special category may also be assigned which indicates that the covariate is unknown. If necessary other methods for missing covariate imputation may be considered. Any additional methods for handling missing covariates will be described in the final report.

3.2.5. Missing Exposure Variable

If the individual PK parameters cannot be derived due to a lack of consistent or sufficient data, the typical values of PK parameters, taking the individual demographic values into account, will be used to derive the corresponding exposure metrics. If the number of subjects with missing exposure is relatively high (higher than 10%), a sensitivity analysis will be conducted by excluding the subjects with missing exposure.

3.2.6. BQL Data

The BQL data may initially be excluded from the estimation of the parameters (the M1 method) but retained in the NONMEM data set. If the amount of BQL is greater than 10%, the likelihood based (M3) method may be considered to evaluate the impact of BQL data on analysis results. [3]

4. DATA ANALYSIS

4.1. Preliminary Population PK model

The sparse PK samples collected in Study 67953964MDD2001 will be evaluated with an existing population PK model, developed on a selection of Phase 1 data, in order to derive individual exposure metrics as per analysis objectives.

A population PK model was published as part of the analysis of receptor-occupancy (RO) data obtained in the clinical study LAF-C using positron emission tomography (PET)[9]. The PK of JNJ-67953964 in the PET study was described by a two-compartment distribution model with a first order absorption including 9 transit compartments. As the PK data in the PET study was limited to 24 hours, it was clear that the elimination was not captured well with this data. Therefore, this model was then updated with the data of the two phase 1 studies available, LAF-A (single doses of 2 to 60 mg) and LAF-B (daily doses of 2, 10 or 35 mg up to 14 days). The preliminary updated model consisted of 6 transit-absorption compartments and inter-individual variability on relative bioavailability F. Parameter estimates of the preliminary updated population PK model are summarized in Table 3. Due to the limited dataset (n=71 subjects, 56 males and 15 females), no covariate analysis was performed. In case a further updated population PK model becomes available by the time of conducting the analysis, the updated model may be used and the details of the model will be provided in the report.

Table 3: **Parameters Estimates of Preliminary Updated Population PK Model**

	Updated model 6 transit-cmt (data LAF-A,-B,-C)	
Parameter (Units)	**Estimate (RSE,%)**	**IIV (%)**
CL/F (L/h)	37.6 (4.81)	28.6
V_c/F (L)	399 (5.54)	22.4
Q/F (L/h)	48.6 (6.46)	-
V_p/F (L)	847 (6.16)	-
KA (/h)	5.36 (3.25)	23.6
F	1 FIX	26.3
RUV (CV%)	0.161 (10.5)	40.1

IIV= inter-individual variability (%); RSE= residual standard error; CV = coefficient of variation; CL/F = apparent clearance; V_c/F = apparent central volume of distribution; Q/F = apparent intercompartmental clearance; V_p/F = apparent peripheral volumes of distribution; KA = absorption rate constant; RUV = residual unexplained variability.

4.2. Analysis Overview

The analysis will consist of the following steps:

1. **Exploratory Analysis**: A graphical analysis will be initially performed to explore baseline covariates and their correlations, JNJ-67953964 plasma concentration data, and change from baseline MADRS and SHAPS total score data collected in Study 67953964MDD2001 stratified by lead-in placebo response;
2. **External Evaluation of the Population PK Model**: An external evaluation of the preliminary updated population PK model will be performed to assess the predictive performance of this population PK model for the patient population in 67953964MDD2001. GoF plots, VPC's, and pcVPC's will be used as external evaluation methods. Refinements of the preliminary population PK model structure may be performed in case the external evaluation is unsuccessful and therefore modifications to the model are required to adequately describe the both the Phase 1 and the current 67953964MDD2001 data;
3. **Determination of Individual Population PK Parameter Estimates**: The individual population PK parameter estimates will be obtained from the population PK model obtained from the previous steps. A graphical covariate analysis will be performed to explore potential parameter-covariate relationships. Covariates that become significant and clinically relevant will be incorporated into the model.;
4. **Derivation of Individual Exposure Parameters**: Using the individual population PK parameter estimates, the individual estimates of the area under the plasma concentration time profile of JNJ-67953964 over 24 hours ($AUC_{0\text{-}24h}$), maximum JNJ-67953964 plasma concentration (C_{max}) and the pre-dose JNJ-67953964 plasma concentration (C_{0h}) will be derived for each visit in all subjects from Study 67953964MDD2001;
5. **Exploration of Relationship between Exposure and MADRS and SHAPS**: Exploratory analyses will be performed to graphically inspect the response variables. During the analyses, at minimum, the following graphs will be explored: individual $AUC_{0\text{-}24h}$ versus MADRS and SHAPS total score, both absolute and change from baseline. Correlation between MADRS and SHAPS total scores. Exploratory plots will be stratified by lead-in placebo-response and by visit. The exposure-response analysis (step 6 and 7) will be performed for the efficacy endpoints if the exploratory analysis shows a relationship in exposure-efficacy;
6. **MADRS and SHAPS PK/PD Modelling**: The change from baseline MADRS and SHAPS total score will be modelled separately using specific parameters for placebo effect, and drug effect, using individual JNJ-67953964 exposure estimates in the drug effect sub-model. Baseline scores, co-medication, gender, race and age at baseline will be tested as potential covariates. Primary analysis on MADRS will be performed on the enriched population (lead-in non-responders). In case no effect on MADRS is found, change from baseline SHAPS total scores will be analyzed on the full dataset. If appropriate, the analysis on MADRS may be repeated on the full dataset, where both lead-in placebo response as well as baseline SHAPS total score will be tested as covariate in the model;
7. **Simulations of change in MADRS and SHAPS:** Based on the final PK/PD model (including covariates, if any), model based simulations of the drug effect on MADRS and SHAPS change from baseline (i.e. net MADRS/SHAPS change from baseline after correction for placebo response) will be generated;

8. **Exploration of Exposure versus Safety Parameters:** Exploratory bar plots of AE grade versus exposure quantiles will be generated for the AE's of interest: pruritis and GI complaints. Other AE's with one or more observations of grade 3 or higher may be included in the exploratory analysis as well. If appropriate, a logistic regression may be used to describe the relationship between exposure and the occurrence of an AE.
9. **Reporting**: Prepare the report in accordance with the FDA and EU guidance on population PK.[1,2]

4.3. Exploratory Analysis

The aim of the exploratory data analysis will be twofold: (i) graphical presentation of the data in order to define the range of concentrations, guide the structural model considerations, and facilitate outlier identification; (ii) examination of covariate correlations which may help in building a covariate sub-model and avoid confounding bias.

Individual, and mean or median, plasma concentration – time profiles will be plotted on linear-linear and logarithmic-linear scales after stratification by lead-in placebo response, SSRI or SNRI co-medication and other appropriate covariates. Data points will be considered as potential outliers if they substantially deviate from adjacent points in the concentration-time profiles and may be omitted from the model building (Section 4.4.2).

In addition, the exploratory graphical analysis of every quantitative covariate will consist of a histogram, box plots and plots of quartiles of covariate distributions and quantiles of standard normal distribution (QQ plot). Summary statistics of each quantitative covariate by study will be provided. Moreover, correlations between quantitative covariates and boxplots for every quantitative covariate against every categorical covariate will be explored.

4.4. Population PK Model Development

4.4.1. External Evaluation of the Preliminary Updated Population PK Model

An external model evaluation will be performed to assess the predictive performance of the preliminary updated population PK model for the current analysis dataset. For this purpose, the following diagnostics will be used:

- Visual Predictive Check (VPC) and Prediction Corrected Visual Predictive Check (pcVPC). The VPC will be performed to provide visual comparison between distributions of simulated data using the previously developed model with the analysis dataset. The pcVPCs differs from traditional VPC in that the dependent variable has been subjected to a prediction correction before the statistics are calculated. Prediction correction aims to correct for the differences within a bin coming from different independent variables in the model and hence, clearly diagnose model misspecifications in both fixed and random effects. In the VPC, the 5th, 50th, and 95th percentiles of the observed data will be compared with the model-based predicted percentiles for each bin across time and replicates. A total of 1,000 replicates of the analysis dataset will be generated from the preliminary population PK model. Uncertainty in parameters estimates will not be considered in this analysis.

- Goodness-of-fit (GoF) plots: A maximum a posteriori (MAP) estimation using the preliminary population model as prior information will be used to estimate the individual population PK model parameters for subjects included in Study 67953964MDD2001. This analysis will be conducted using the MAXEVAL=0 option in NONMEM. The following goodness-of-fit plots will be generated in order to assess the deviation of population and individual predictions from the observed data:
    - Observations vs population predictions (PRED);
    - Conditional weighted residuals vs PRED and vs time since last dose;
    - Observations vs individual predictions (IPRED);
    - Individual weighted residuals vs IPRED and vs time since last dose;
- Numerical Predictive Check (NPC). The NPC will be performed on the mean and the standard deviation (SD) of the exposure metrics (AUC_{24h} and C_{0h}), since these reflect the central tendency and the variability of the exposure metrics. Within each replicate, the mean and SD of the exposure metrics to be used in the ER analysis will be computed. The model-based distribution of the mean and SD of the exposure metrics across replicates will be obtained and its 2.5th and 97.5th percentile will be used to calculate the lower and upper limit of the 95% confidence interval (CI) of the model-based predicted mean and SD of the exposure metrics, which will be then compared to the actual metric of exposure obtained from the Study 67953964MDD2001. Based on the parameter estimates of the previously developed model, 1000 replicates of the analysis dataset will be simulated.

Adequacy of the model will be assessed by the ability of the model to capture the central tendency and the variability of the data (as attested by the VPC/pcVPC plots) and to provide population and individual predictions without significant bias (confirmed by the GoF plots).

If the external evaluation is unsuccessful, potential refinements of the preliminary population PK model (e.g. modifications of the model structure, re-estimation of population parameters, addition of study-specific factors, etc) will be evaluated in order to adequately describe the data from Study 67953964MDD2001 and the three Phase 1 studies, LAF-A, LAF-B and LAF-C. If a model update is performed, the criteria described in Section 4.9 may be used to compare different candidate models.

4.4.2. Identification of Outliers

An outlier is defined as an aberrant observation that significantly deviates from the rest of the observations in a particular subject or as a subject when all observations for that subject are aberrant. Outliers may be excluded from the analysis as they are known to have negative impact on the convergence and/or introduce bias in parameter estimates. The outlier detection in the full PK profiles will be based primarily on visual examination of individual and pooled concentration-time profiles. Data points will be considered as potential outliers if they substantially deviate from adjacent points in the concentration-time profiles and if their conditional weighted residual is large,

eg, greater than +/- 6 units. Only the observations that meet both criteria will be identified as outliers. The observations will be excluded from the analysis by flagging them with "C" in the NONMEM dataset. In a subsequent step, it may be investigated if the outliers influence the population and individual population PK model parameter estimates.

4.4.3. Covariate Analysis

The model described above (i.e. previously developed preliminary PK model or updated PK model) may constitute the base model for covariate model development. The basis of the covariate model should be the clinical significance of the covariate effects rather than their statistical significance. The model building will consist of a number of steps based on the guidance by various regulatory authorities[1,2,16];

1. A list of covariate/parameter pairs that are physiologically plausible are selected from exploratory plots of EBE vs covariates and based on generalized additive models (GAM)[6] on the regression between each EBE and the covariates. Only covariates that are statistically significant ($p < 0.001$) with model parameters will be considered as potentially clinically relevant and will be further evaluated. Covariates will include gender, race, age, body weight, albumin and creatine clearance at baseline. If a candidate covariate can be represented as either a categorical or continuous covariate, the continuous covariate is usually preferred.
2. Trim the list using the following criteria:
    a. When two or more covariates have correlation greater than 0.3 the most physiologically plausible should be retained and the others discarded because retaining them gives rise to the co-linearity problem.
    b. Remove covariates having insufficient sample sizes, ie, represented by less than 20 subjects per parameter.[20,21]
    c. Overall number of subjects vs. number of covariate evaluations (number of covariate parameters) ≥ 10.[19]
3. Fit the full model.[20,21] If the full model does not converge, then the forward stepwise selection method can be taken based on a p-value < 0.01.
4. The full covariate model from step 3 may be reduced based on the point estimates of the magnitude of the effect of the covariate on the PK parameter using a clinically meaningful threshold (if available), to obtain the final covariate model. If deemed necessary, this step may be preceded by backward elimination using a more stringent nominal p-value of 0.001.
5. A diagnostic plot should be made. It is useful to generate a forest plot[7] or equivalent for the final covariate model to assist identification of clinically relevant covariates. Statistical tests on empirical Bayes' estimates (EBE's) are preferred over exploratory plots of EBE's versus the covariates if the shrinkage is large (eg, >35%).[17,18]

A discussion of the physiological plausibility and clinical relevance of the final covariate model may be included in the discussion section of the report. We must take into consideration that the model is based on an association between the PK parameters and the covariates which can only be interpreted as causative if there are good scientific reasons for doing so.

4.4.4. Refining the Covariance Structure

Correlation between PK parameters may be tested after all significant fixed covariate effects have been included in the model. The individual ETAs will be examined graphically by plotting each ETA against all others. If visual inspection of plots reveals any correlation, the corresponding block may be introduced into the OMEGA matrix to test its significance using the likelihood ratio test. If implementing a correlation significantly improves the fit, the block will be kept in the model. The process will be repeated until no further improvement of the fit can be achieved. A model with a full block of correlations between random effects will be used as a reference to determine the maximum possible improvement by optimizing covariance structure.

4.5. Determination of Individual Population PK Parameter Estimates

The individual population PK parameter estimates of $AUC_{0\text{-}24h}$, C_{max} and the pre-dose JNJ-67953964 plasma concentration (C_{0h}) will be calculated for each subject at each visit either by fixing the population parameters of the full covariate population PK model.

Correlation between population PK parameters will be assessed.

4.6. MADRS and SHAPS PK/PD Modelling

Exploratory plots of individual $AUC_{0\text{-}24h}$ versus MADRS and SHAPS total score, both absolute and change from baseline, stratified by lead-in placebo-response and by visit will be created. The exposure-response analysis will only be performed for the efficacy endpoints if the exploratory analysis shows a relationship in exposure-efficacy.

The MADRS and SHAPS total score data will be modelled using specific parameters for baseline response, placebo effect, and drug effect, according to the following general equation:

$$y_{ij} = (\theta_1 v_1 + \theta_2 v_2 + \theta_3 v_3 + \theta_4 v_4 + \theta_5 v_5 + \alpha_i) + f_i(v_j, C_i) + \varepsilon_{ij}$$

where y_{ij} represents the change from baseline MADRS or SHAPS total score for the i-th subject at the j-th time point (j=1..5 for the 5 post-baseline visits in Week 1, 3, 4, 5 and 6), $\theta_{1\text{-}5}$ represent the fixed effects for the placebo response at the post-baseline visits, i.e. j=1..5 (with $v_{1\text{-}5}$ denoting indicator variables with value 1 when j is equal to Treatment Week 1, 3, 4, 5 and 6), α_i represents the random effect parameter for non-drug-related response, $f_i(v_j, C_i)$ representing the concentration-effect relationship for JNJ-67953964 in the i-th subject at the post-baseline visits, i.e. j=1..5 as a function of the exposure metric C_i, and ε_{ij} represents the residual variability associated to measurement y_{ij}. Baseline is defined as treatment baseline, i.e. last observation before the first dose.

The inter-individual variability (IIV) random effect α_i, and any random effect within f_i will be assumed to be normally-distributed, zero-mean, uncorrelated random variables. The residual variability random effects ε_{ij} will be assumed to be normally-distributed, zero mean, uncorrelated random variables that are also uncorrelated with respect to α_i, and any random effect within f_i. Alternative distributions for the IIV and the residual variability random effects may be considered if needed. If warranted by the data, parametric functions of time (e.g. linear, exponential) may be used to describe the placebo effect.

The exposure metrics to be used in the PK/PD model will be AUC_{24h} (see Section 4.5). Additional exposure metrics may be tested if the R^2 of the correlation between PK parameters is less than 0.8.

In case of C_{0h}, observed pre-dose exposure may be used as an alternative to the model-estimated C_{0h}.

The drug effect sub-model may be parametrized as a linear, or if the exposure range allows, E_{max}, sigmoid E_{max}, or exponential function, as determined by model building criteria (Section 4.9). In case a delay in onset of drug effect will be observed during the exploratory analysis, the delay will be fit using an appropriate delay function, such as a sigmoid[13]. Additional functional forms of the drug effect sub-models may be tested. Baseline MADRS or SHAPS will be tested as covariate on both drug-related and drug-non-related response in order to assess the potential influence of higher/lower baseline disease severity on MADRS and SHAPS change. Gender, race, and age at baseline will also be tested. Lead-in placebo response will be tested as covariate on models based on the full dataset for change from baseline MADRS scores. Lead-in placebo response will not be tested as covariate for change from baseline SHAPS models, as no effect was observed on SHAPS during the lead-in period based on blinded data. Additional parameter-covariate relationships may be tested if required.

Primary analysis on MADRS will be performed on the enriched population (lead-in non-responders). In case no effect on MADRS is found, change from baseline SHAPS total scores will be analyzed on the full dataset. If appropriate, the analysis on MADRS may be repeated on the full dataset, where both lead-in placebo response as well as baseline SHAPS total score will be tested as covariate in the model.

Change from baseline MADRS or SHAPS total scores obtained during the withdrawal period (Day 78) may be explored and included in the model as function of exposure if deemed appropriate.

4.7. Simulations

Based on the final PK/PD model (including covariates, if any), model-based simulations of placebo corrected change from baseline in MADRS/SHAPS will be generated. The following simulations will be performed:

a) Population distribution of the MADRS and SHAPS change from baseline and of the drug effect on MADRS and SHAPS at Week 6 vs AUC;

b) Probability to achieve a drug effect on MADRS and SHAPS of at least 1, 2, or 3 points drop at Week 6 in the population;

c) Point estimate and 90% confidence interval (CI) for the MADRS and SHAPS change from baseline and for the drug effect on MADRS and SHAPS at Week 6 vs AUC for the population studied;

d) Model-based MADRS and SHAPS change from baseline vs time by lead-in placebo-response.

Simulations (a), (b) and (d) will be performed using 10,000 subjects per dose level in order to adequately reflect PK and PD variability in a large population. For this purpose, interindividual variability in PK and in PD parameters, as well as residual variability in MADRS and SHAPS, will be included in the simulations. Uncertainty of model parameter estimates will not be included. Simulations will be performed at the 10 mg qd dose level. Other dosing regimen may be included if deemed appropriate. The simulations will be summarized as median, 5th and 95th percentiles of the population. Simulations (a), (b) and (c) may be repeated for additional treatment days of

interest. When appropriate, simulations will be performed in sub-populations based on specific selection criteria, such as lead-in-placebo-response or baseline SHAPS scores.

4.8. Exploration of Exposure - Safety Parameters

Based on the clinical relevance, the AE data for gastrointestinal disorders will be dichotomized into presence or absence of an AE grade ≥ 3 at any visit postdose up to the last treatment day, while for pruritus and specific subclasses of gastrointestinal AE's (e.g. diarrhea, constipation, abdominal pain) dichotomization will be based on any occurrence at any visit postdose up to the last treatment day (Day 22 to Day 64). JNJ-67953964 exposure metrics will be classified into 3 or 4 categories dependent on the number of subjects per quantile. Similarly, an additional category will be included for the placebo-randomized subjects; in this case the exposure metrics will be assigned to a value of zero. Exploratory bar plots of number of subjects with an AE versus exposure groups will be generated for the AE's of interest pruritis and GI complaints. If appropriate additional plots may be generated for other AE's with at least one observation of grade 3 or higher. If appropriate, a logistic regression may be used to describe the relationship between exposure and the occurrence of an AE. The exposure metrics to be used in the PK-safety evaluation will be C_{max} (see Section 4.5). Additional exposure metrics may be tested if the R^2 of the correlation between PK parameters is less than 0.8.

4.9. Model Evaluation/Qualification

Model evaluation/qualification assesses the extent of any mismatch between the model and the data that it is describing. The exact procedures employed depend on the data and models and can therefore not be prescribed.

The following plots may be examined to assess model evaluation/qualification:

- Plots with predicted versus observed values of the response variable(s);
- Plots with predicted values superimposed on plots of the data;
- Various plots of residuals;
- Plots of random effects versus covariates;
- Visual or/and numerical predictive checks (VPC or/and NPC);
- Other plots may be examined as required.

4.9.1. Statistical Considerations in Case of Model Update

The principle of parsimony will be applied, meaning that the simplest model that adequately fulfils the analysis objective will be preferred. The statistical criteria described below will be used to compare different candidate models by NONMEM:

- To accommodate for multiple comparisons testing, inherent in population PK model development, a 6 points reduction of the objective function value for one additional parameter (either structural or random) in nested models, theoretically coinciding with $P \leq 0.01$ in a Chi-square (χ^2) test, will be deemed significant during model development.
- For non-nested models, the appropriate Akaike's Information Criterion (AIC) or alternative model selection criteria such as the Bayesian Information Criterion (BIC) may be used.[4]

The statistical criteria outlined below will be used for model assessment

- The standard error of a structural parameter estimates reported by NONMEM should preferably be less than 50% of the estimated parameter value. This would imply that zero is excluded from the 95% CI of the parameter estimate, assuming normality.
- The correlation between parameter estimates (structural and stochastic) reported by NONMEM in the correlation matrix of the model output, should lie between -0.95 and 0.95
- The values estimated for η should be adequately centered around zero (reported p-value in the NONMEM output file should be larger than 0.05).
- Shrinkage of the random effects should preferably be below 30% (η-shrinkage and ε-shrinkage).[14]

4.10. Computer Software

Plasma concentration-time data will be used for non-linear mixed effect modeling using NONMEM (ICON plc).[11] The first-order conditional estimation method (FOCE) estimation method will be used. The INTERACTION option will be used when appropriate. However, other estimation methods available in NONMEM may be used if deemed necessary. The NONMEM analysis is performed in a validated environment, the High Performance Pharmacometric Platform (HP3) based on Good Automated Manufacturing Practice (GAMP) and in accordance with 21 CFR Part 11 and Good Clinical Practice (GCP) regulations.

Post-processing of the NONMEM analysis results will be carried out in R (Version 3.3.1 or higher)[12] or any other validated software.

4.11. Report

A final report will be prepared in accordance with the FDA and EU guidances[1,2] on population PK using the internal Janssen R&D report template. The final analysis report should always be reviewed according to the Overarching PM SOP and the internal Janssen R&D QC templates for analysis and report.

Per the internal Janssen R&D Job Aid for e-Submission, Janssen R&D will provide the NONMEM datasets in .xpt format. Janssen R&D will supply the NONMEM control streams and outputs in .pdf format.

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