STATISTICAL ANALYSIS PLAN
MEIN/18/DEX-LBP/001

A randomized, double-blind, placebo-controlled, parallel arm group study to evaluate the analgesic efficacy and safety of **D**exketoprofen trometh**A**mol a**N**d **T**ramadol hydrochloride oral fix**E**d dose combination on moderate to severe acute pain in patients with acute low back pain - DANTE

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VERSION NUMBER AND DATE: V1.0, 04JUL2022

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0(Dated 04Jul2022) for Protocol MEIN/18/DEX-LBP/001

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version	Reviewed by
Version 1.0	04Jul2022	Aswin Nair	Not Applicable – Draft Version	

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ANCOVA	Analysis of covariance
BOCF	Baseline observation carried forward
CMH	Cochran–Mantel–Haenszel
DKP.TRIS	Dexketoprofen trometamol
eCRF	Electronic case report forms
ITT	Intention-to-treat
LBP	Low back pain
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical Rating Scale
PAR	Pain relief
PGE	Patient Global Evaluation
PI	Pain intensity
PP	Per-protocol
RM	Rescue medication
RMQ	Roland Morris Disability Questionnaire
SAE	Serious adverse event
SAP	Statistical analysis plan
SOP	Standard operating procedures
SPID	Summed Pain Intensity Difference
TEAE	Treatment emergent adverse event
TOTPAR	Total pain relief
TRAM.HCl	Tramadol hydrochloride
TSQM	Treatment Satisfaction Questionnaire for Medication
VAS	Visual Analogue Scale
VRS	Verbal rating scale

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol MEIN/18/DEX-LBP/001. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. This statistical analysis plan (SAP) is based on protocol version 2.0 (Amendment 1), dated 13 September 2021.

2. STUDY OBJECTIVES AND ESTIMANDS

2.1. PRIMARY OBJECTIVE

The primary objective is to evaluate the analgesic efficacy of DKP.TRIS/TRAM.HCl fixed combination versus placebo in moderate to severe acute low back pain after the first dose (first 8 hours).

2.2. SECONDARY OBJECTIVES

The secondary objectives are,

- To evaluate the analgesic efficacy of DKP.TRIS/TRAM.HCl fixed combination versus TRAM.HCL 100 mg in moderate to severe acute low back pain after the first dose (first 8 hours).
- To evaluate the analgesic efficacy of DKP.TRIS/TRAM.HCl fixed combination in moderate to severe acute low back pain versus TRAM.HCl 100 mg after multiple doses (from t8h until day 5).
- To assess the safety and tolerability of DKP.TRIS/TRAM.HCl fixed combination after single and multiple doses.

2.3. ESTIMANDS

The primary, and secondary estimands to support regulatory decisions are described in the following table:

Table A: List of Estimands

Estimand	Definition	Attributes			
		Population	Variable/Endpoint	Intercurrent event handling strategy	Population-level summary measure
Single Dose Phase					
Primary Estimand	Efficacy of DKP.TRIS/ TRAM.HCl fixed combination versus placebo in moderate to severe acute low back pain after the first dose (first 8 hours).	mITT Population (All patients randomized and satisfies the randomization ratio 4:4:1:1)	Time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose	Composite Strategy. Initiation of rescue medication (RM). Scores after RM return to baseline level. This assumes that the treatment has no impact on the primary endpoint. The patients are censored at the point of first intake of rescue medication (i.e. considered as no longer at risk of an event).	Hazard Ratio
Primary Estimand Sensitivity 1		mITT Population (All patients randomized and satisfies	Time to first achieve an NRS-PI score <4 or a pain intensity reduction of	Treatment Policy Strategy Initiation of rescue medication.	Hazard Ratio

		the randomization ratio 4:4:1:1)	≥30% from drug intake till 8 hours after the first dose	Values collected are used regardless of whether the RM is taken without imputation. This reflects the assumption that rescue mediation does not influence the primary endpoint	
Primary Estimand Sensitivity 2		mITT Population (All patients randomized and satisfies the randomization ratio 4:4:1:1)	Time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose	Hypothetical Strategy Scenario envisaged in which the intake of rescue medication would not occur. Values collected for the six hours after the RM intake will be considered as missed and imputed by using a multiple imputation approach. If a missing at random (MAR) pattern of missing data is detected, missing values will be replaced using a	Hazard Ratio

				multiple imputation approach.	
Primary Estimand Sensitivity 3		ITT Population (All patients randomized)	Time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose	Composite Strategy. Initiation of rescue medication (RM). Scores after RM return to baseline level. This assumes that the treatment has no impact on the primary endpoint. The patients are censored at the point of first intake of rescue medication (i.e. considered as no longer at risk of an event).	Hazard Ratio
Primary Estimand Sensitivity 4		ITT Population (All patients randomized)	Time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose	Treatment Policy Strategy Initiation of rescue medication. Values collected are used regardless of whether the RM is taken without imputation. This	Hazard Ratio

				reflects the assumption that rescue mediation does not influence the primary endpoint	
Primary Estimand Sensitivity 5		ITT Population (All patients randomized)	Time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose	Hypothetical Strategy Scenario envisaged in which the intake of rescue medication would not occur. Values collected for the six hours after the RM intake will be considered as missed and imputed by using a multiple imputation approach. If a missing at random (MAR) pattern of missing data is detected, missing values will be replaced using a multiple imputation approach.	Hazard Ratio
Primary Estimand Sensitivit		PP Population (All patients randomized	Time to first achieve an NRS-PI score <4 or a pain	Composite Strategy. Initiation of	Hazard Ratio

y 6		without any major PDs that affect primary efficacy analysis)	intensity reduction of ≥30% from drug intake till 8 hours after the first dose	rescue medication (RM). Scores after RM return to baseline level. This assumes that the treatment has no impact on the primary endpoint. The patients are censored at the point of first intake of rescue medication (i.e. considered as no longer at risk of an event).	
Primary Estimand Sensitivity 7		PP Population (All patients randomized without any major PDs that affect primary efficacy analysis)	Time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose	Treatment Policy Strategy Initiation of rescue medication. Values collected are used regardless of whether the RM is taken without imputation. This reflects the assumption that rescue mediation does not influence the primary endpoint	Hazard Ratio

Primary Estimand Sensitivity 8		PP Population (All patients randomized without any major PDs that affect primary efficacy analysis)	Time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose	Hypothetical Strategy Scenario envisaged in which the intake of rescue medication would not occur. Values collected for the six hours after the RM intake will be considered as missed and imputed by using a multiple imputation approach. If a missing at random (MAR) pattern of missing data is detected, missing values will be replaced using a multiple imputation approach.	Hazard Ratio
Primary Estimand Sensitivity 9	Efficacy of DKP.TRIS/ TRAM.HCl fixed combination versus placebo in moderate to severe acute	mITT Population (All patients randomized and satisfies the randomization ratio 4:4:1:1)	Time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose	Composite Strategy. Initiation of rescue medication (RM). Scores after RM return to baseline level. This assumes that the	Hazard Ratio

	low back pain after the first dose (first 8 hours).			treatment has no impact on the primary endpoint. The patients are censored at the point of first intake of rescue medication (i.e. considered as no longer at risk of an event). The IRT collected strata will be replaced by CRF collected/derived strata	
Primary Estimand Sensitivity 10	Efficacy of DKP.TRIS/ TRAM.HCl fixed combination versus placebo in moderate to severe acute low back pain after the first dose (first 8 hours).	ITT Population (All patients randomized)	Time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose	Composite Strategy. Initiation of rescue medication (RM). Scores after RM return to baseline level. This assumes that the treatment has no impact on the primary endpoint. The patients are censored at the point of first intake of rescue medication (i.e.	Hazard Ratio

				considered as no longer at risk of an event). The IRT collected strata will be replaced by CRF collected/derived strata	
Primary Estimand Sensitivity 11	Efficacy of DKP.TRIS/ TRAM.HCl fixed combination versus placebo in moderate to severe acute low back pain after the first dose (first 8 hours).	PP Population (All patients randomized without any major PDs that affect primary efficacy analysis)	Time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose	Composite Strategy. Initiation of rescue medication (RM). Scores after RM return to baseline level. This assumes that the treatment has no impact on the primary endpoint. The patients are censored at the point of first intake of rescue medication (i.e. considered as no longer at risk of an event). The IRT collected strata will be replaced by CRF collected/derived strata	Hazard Ratio

Primary Estimand Sensitivity 12	Efficacy of DKP.TRIS/ TRAM.HCl fixed combination versus placebo in moderate to severe acute low back pain after the first dose (first 8 hours).	mITT Population (All patients randomized and satisfies the randomization ratio 4:4:1:1) and having same strata collected in both CRF and IRT	Time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose	Composite Strategy. Initiation of rescue medication (RM). Scores after RM return to baseline level. This assumes that the treatment has no impact on the primary endpoint. The patients are censored at the point of first intake of rescue medication (i.e. considered as no longer at risk of an event).	Hazard Ratio
Primary Estimand Sensitivity 13	Efficacy of DKP.TRIS/ TRAM.HCl fixed combination versus placebo in moderate to severe acute low back pain after the first dose (first 8 hours).	ITT Population (All patients randomized) and having same strata collected in both CRF and IRT	Time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose	Composite Strategy. Initiation of rescue medication (RM). Scores after RM return to baseline level. This assumes that the treatment has no impact on the primary endpoint. The patients are censored at the	Hazard Ratio

				point of first intake of rescue medication (i.e. considered as no longer at risk of an event).	
Primary Estimand Sensitivity 14	Efficacy of DKP.TRIS/ TRAM.HCl fixed combination versus placebo in moderate to severe acute low back pain after the first dose (first 8 hours).	PP Population (All patients randomized without any major PDs that affect primary efficacy analysis) and having same strata collected in both CRF and IRT	Time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose	Composite Strategy. Initiation of rescue medication (RM). Scores after RM return to baseline level. This assumes that the treatment has no impact on the primary endpoint. The patients are censored at the point of first intake of rescue medication (i.e. considered as no longer at risk of an event).	Hazard Ratio

3. STUDY DESIGN

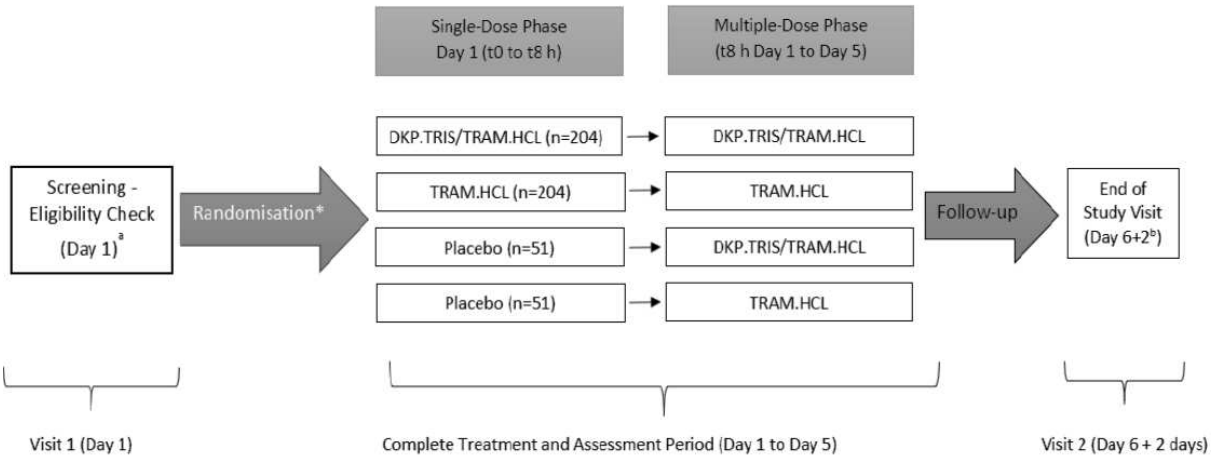
3.1. GENERAL DESCRIPTION

This is a Phase IV, multicenter, randomized, double-blind, double-dummy parallel group, placebo-controlled study encompassing 2 study phases: a single-dose phase (first 8 hours) and a multiple-dose phase starting after the single-dose phase (from 8th hour until Day 5) aimed to investigate the efficacy of DKP.TRIS/TRAM.HCl fixed combination in moderate to severe acute lower back pain

(LBP).

In the single-dose phase the patients will receive a single dose treatment, consisting of 1 film-coated tablet and 2 capsules which must be orally administered together at the same time (Day 1) and according to Investigator's instructions. The multiple-dose phase will begin 8 hours after the first dose. The patients assigned to DKP.TRIS/TRAM.HCl fixed combination or TRAM.HCL 100 mg during the single-dose phase will continue to receive the same treatment during the multiple-dose phase; however, the patients assigned to receive placebo during the single-dose phase will either receive DKP.TRIS/TRAM.HCl fixed combination or TRAM.HCL 100 mg during the multiple-dose phase. The study is considered completed when the last patient's last study visit has occurred. 510 eligible patients will be randomized in a 4:4:1:1 ratio to 1 of the 4 possible treatment arms. Data are collected through a combination of e-Diary and data entered through the eCRF at site. All efficacy related, Rescue medication and study medication data are collected through e-diary.

3.2. STUDY SCHEME



*Subject will be randomized in a 4:4:1:1 ratio to 1 of the 4 possible treatment arms.

[a] A follow up phone call after Visit 1 will be scheduled only in case of abnormality and clinically relevant laboratory test according to the investigator is observed in laboratory test results performed at Screening.

[b] A follow up phone call after Visit 2 will be scheduled only in case of abnormality and clinically relevant laboratory test according to the investigator is observed in laboratory test results performed at the end of study visit (Visit 2).

Figure 1: Overview of Trial Design

3.3. SCHEDULE OF EVENTS

Schedule of events can be found in Section 4.1 of the protocol.

3.4. CHANGES TO ANALYSIS FROM PROTOCOL

- As per protocol, the definition of Per Protocol Population is "All patients of the ITT population who have not experienced major protocol violations that could affect the analyses". In SAP, this has been updated to,
  "The per-protocol (PP) population will contain all patients in the ITT who have not experienced major protocol violations that could affect the primary efficacy analysis".
- Randomization eliminates a systematic difference between subjects in treatment groups inducing approximate balance with respect to covariates, both observed and unobserved. The correct proportion of patients among treatment groups represents a fundamental element to increase the efficiency of the study. Not respecting the study protocol randomization scheme can have consequences for statistical power that is directly related to statistical efficiencies. In this study a 4:4:1:1 ratio produces a justified post-randomization belief regarding allocation to the investigational treatments versus placebo. However, one of the four treatment arms randomized more patients than initially designed in the protocol, leading to an unbalanced proportion among the four arms of the study. So, an additional analysis population, modified Intent-to-Treat (mITT) is added in the study which maintains the 4:4:1:1 ratio of patients across the treatment groups. The definition of mITT population is,
- "The modified intent-to-treat population will contain the first cohort of 510 patients randomized to the four treatment groups((204 patients in the DKP.TRIS/TRAM.HCl + DKP.TRIS/TRAM.HCl arm, 204 patients in the TRAM.HCl + TRAM.HCl arm, 51 patients in the placebo + DKP.TRIS/TRAM.HCl arm and finally 51 patients in the placebo + TRAM.HCl arm)." Efficacy analyses will be performed using the mITT population (primary efficacy dataset), ITT population and PP population.

4. PLANNED ANALYSES

A final Analysis after database lock (DBL) is planned for this study.

4.1. Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this Statistical Analysis Plan, Database Lock, Sponsor Authorization of Analysis Sets and Unblinding of Treatment.

5. Analysis Population

Agreement and authorization of patients included/excluded from each analysis set will be conducted prior to database lock and the unblinding of the study.

5.1. Intent-to-Treat [ITT] Population

The intent-to-treat (ITT) population will contain all patients randomized to any of the treatment groups. For analyses and displays based on ITT, patients will be classified according to randomized treatment.

5.2. Modified Intent-to-Treat [mITT] Population

The modified intent-to-treat population will contain the first cohort of 510 patients randomized to the four treatment groups ((204 patients in the DKP.TRIS/TRAM.HCl + DKP.TRIS/TRAM.HCl arm, 204 patients in the TRAM.HCl + TRAM.HCl arm, 51 patients in the placebo + DKP.TRIS/TRAM.HCl arm and finally 51 patients in the placebo + TRAM.HCl arm). In this cohort of patients, the randomization scheme 4:4:1:1 was completely respected. For analyses and displays based on mITT, patients will be classified according to randomized treatment.
The patients will be included in the mITT based on the randomization order. i.e., the first 204 patients randomized to active arm and the first 51 patients randomized to Placebo arm will be considered in the mITT set.

5.3. Safety [SAF] Population

The safety (SAF) population will contain all patients in the ITT who have received at least 1 dose of the study treatment.
If there is any doubt whether a patient was treated or not, they will be assumed treated for the purposes of analysis. Patients will be assigned to the treatment received, for each category in case

the treatment received differs from that randomized.

5.4. Per Protocol [PP] Population

The per-protocol (PP) population will contain all patients in the ITT who have not experienced major protocol violations that could affect the primary efficacy analysis. Protocol violations which have a major distorting influence on the primary endpoints will result in patients being excluded from the PP. PDs identified during the clinical conduct of the study, as authorized in the final PD log, will also be taken into consideration in the final assignment of patients to the analysis sets.
Patients will be assigned to the treatment received, for each category in case the treatment received differs from that randomized.

Reasons for exclusion can be, but not limited to:

- Non-compliance with the inclusion or exclusion criteria.
- Insufficient essential efficacy data for the primary analysis.
- Intake of prohibited medication.
- Non-compliance with the study treatment.
- Non-compliance with time window for the primary efficacy data.
- Non-compliance with randomization criteria.

6. General Considerations

6.1. Reference Start Date and Study Time

Study Day and Time will be calculated from the reference start date/time and will be used to show start/stop day / time of assessments and events as applicable.

Reference start date/time is defined as the day/time of the first dose of study medication, (Day 1 is the day of the first dose of study medication) and will appear in every listing where an assessment date/time or event date appears.

- If the date and time of the event is on or after the reference date and time, then:
- Study Day and Time = (date and time of event – reference date and time+1).
- If the date of the event is prior to the reference date, then:
- Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding

durations will appear partial or missing in the listings.

Multiple dose phase start date/time will be assessed based on the date/time of second dose administration. If a patient skipped the second dose at 8th hour and took dose at 16th hour, then the multiple dose phase start date/time for that patient will be 16th hour.

6.2. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date/time (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered baseline, but Adverse Events (AEs) and medications commencing on the reference start date/time will be considered post-baseline, unless the start time of the AE/medications is known to be prior to the first dosing of the investigational product.

6.3. Retests, Unscheduled Visits and Early Termination Data

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries. Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. Windowing Conventions and Timepoint Derivation for Questionnaire Data

Timepoint	Questionnaire	Window
0h	Study Medication Use Rescue Medication Use	Open until completed
15min*	NRS-PI VRS-PAR	+/- 7 mins
30min*	NRS-PI VRS-PAR	+/- 7 mins
1h*	NRS-PI VRS-PAR	+/- 15 mins
1.5h*	NRS-PI VRS-PAR	+/- 15 mins
2h*	NRS-PI	+/- 15 mins

	VRS-PAR	
4h*	NRS-PI VRS-PAR	+/- 15 mins
6h*	NRS-PI VRS-PAR	+/- 15 mins
8h*	PGE NRS-PI VRS-PAR Study Medication Use	+/- 35 min
10h	NRS-PI VRS-PAR	+/- 30 min
16h	NRS-PI VRS-PAR Study Medication Use	+/- 30 min
18h	NRS-PI VRS-PAR	+/- 30 min
24h	NRS-PI VRS-PAR Study Medication Use	+/- 30 min
26h	NRS-PI VRS-PAR	+/- 30 min
32h	NRS-PI VRS-PAR Study Medication Use	+/- 30 min
34h	NRS-PI VRS-PAR	+/- 30 min
40h	NRS-PI VRS-PAR Study Medication Use	+/- 30 min
42h	NRS-PI VRS-PAR	+/- 30 min
48h	NRS-PI VRS-PAR Study Medication Use	+/- 30 min
50h	NRS-PI VRS-PAR	+/- 30 min
56h	NRS-PI VRS-PAR	+/- 30 min

	Study Medication Use	
58h	NRS-PI VRS-PAR	+/- 30 min
64h	NRS-PI VRS-PAR Study Medication Use	+/- 30 min
66h	NRS-PI VRS-PAR	+/- 30 min
72h	NRS-PI VRS-PAR Study Medication Use	+/- 30 min
74h	NRS-PI VRS-PAR	+/- 30 min
80h	NRS-PI VRS-PAR Study Medication Use	+/- 30 min
82h	NRS-PI VRS-PAR	+/- 30 min
88h	NRS-PI VRS-PAR Study Medication Use	+/- 30 min
90h	NRS-PI VRS-PAR	+/- 30 min
96h	NRS-PI VRS-PAR Study Medication Use	+/- 30 min
98h	NRS-PI VRS-PAR	+/- 30 min
104h	NRS-PI VRS-PAR RMDQ TSQM PGE	+/- 30 min

* The window period specified in the ERT project design specification document (version 3.0) for the timepoints within the first 8 hours (single dose phase) is very narrow. There are chances to have records for the questionnaire responses a few minutes outside the window period for each of the timepoints since the data is collected through e-diary. So, in order to include the maximum number

of data points in the analysis, without clinically meaningful impact, the window period for the timepoints were extended as follows:

- Timepoints 15min and 30min : Window period extended from +/- 5 min to +/- 7 min
- Timepoints 1h till 6h : Window period extended from +/- 10 min to +/- 15 min
- Timepoint 8h : Window period extended from +/- 30 min to +/- 35 min

The timepoint of each questionnaire will be derived based on the difference between the first treatment administration date/time and the assessment date/time, considering the above-mentioned window period. Any assessment falling out of the window will be considered as unscheduled and will not be considered for the summary or statistical analysis but will be displayed in the listings.
If a patient is having multiple entries with respect to a particular timepoint, then the assessment which is closer to the scheduled date/time of that particular timepoint will be considered. In case if a patient has multiple records at a timepoint which is equidistant from the scheduled time, then the latest record will be considered for the analysis.

6.5. Statistical Tests

The default significant level will be (5%); confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

6.6. Common Calculations

For quantitative measurements, change from baseline (absolute and percentage) will be calculated as:

- Test Value at Visit X – Baseline Value
- (Test Value at Visit X – Baseline Value)/ Baseline Value*100

6.7. Software Version

All analyses will be conducted using SAS Enterprise Guide 8.2.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following covariates/factors will be used in the analyses.

- Treatment
- Baseline PI categories based on NRS scale
  - ≥ 5 to ≤7 (moderate pain)
  - >7 (severe pain)
- Baseline radiculopathy categories based on Quebec Task Force classification35
  - LBP without radiation
  - LBP+ radiation to extremity, proximally
  - LBP+ radiation to extremity, distally
- Baseline Roland Morris Disability Questionnaire score

For further details on statistical models based on the above factors, please refer to section 16.

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally.

7.3. MISSING DATA

Missing safety data will not be imputed. Missing efficacy data will be handled as follows.

Data imputations will be done for Pain intensity (PI) and Pain relief (PAR) assessment under the following circumstances:

- First, for values collected after the rescue medication (RM) intake
- Then, missing data.

For all PI assessments at each timepoint after the first RM intake, PI will return to its baseline level.
Single missing values between measurements will be linearly interpolated using the formula;
$Y = ((X - X1)(Y2 - Y1) / (X2 - X1)) + Y1$
Where, (X1, Y1) = First co-ordinates, (X2, Y2) = Second co-ordinates, X = Target X co-ordinate, Y = Interpolated Y co-ordinate.

If more than one consecutive data are missed, Last Observation Carry Forward (LOCF) method will be applied.
Once imputations are done, the efficacy variables based on PI and PAR assessments (SPID, TOTPAR, etc.) will be re-derived based on the PI and PAR imputed values. Different strategies will be used to handle data imputation. A summary is provided in the table below:

	Values collected after the RM intake	Missing data
Main Analysis	**Single dose phase:** For all PI and PAR assessments at each timepoint after the first RM intake, PI will return to its baseline level and PAR to zero (Baseline Observation Carried Forward [BOCF]). **Multiple-dose phase:** PI and PAR assessments recorded during the 6 hours after the intake of RM (based on the effect of Paracetamol) will be replaced with the last observation carried forward (LOCF) (which should be the one done immediately before RM) or worst observation carried forward (WOCF) in case the assessment immediately before intake is missed.	Single missing values between measurements will be linearly interpolated, if more consecutive data are missed LOCF method will be applied
Sensitivity Analysis 1	Treatment Policy Strategy: values collected are used regardless of whether the RM is taken without any imputation.	No imputation, missing values will not be replaced.
Sensitivity Analysis 2	Hypothetical Strategy: a scenario is envisaged in which the intake of RM would not occur. Values collected for the 6 hours after the RM intake will be considered as missed and they will be imputed by using a multiple imputation approach.	Missing values will be replaced by using a multiple imputation approach.

The intake of RM can be identified from the diary data (Rescue Medication Use).
For duration of disease and birth date, the missing date will not be imputed. Calculation for the partial date is described in Appendix 2

7.4. Multiple Comparisons/ Multiplicity

There is one primary endpoint comparison for superiority (as detailed in Section 16.1.3) for this study. For the switch from non-inferiority to superiority no multiplicity adjustment is needed, since, as stated in CPMP/EWP/482/99, the superiority interpretation of results corresponds to a simple closed test procedure.

7.5. Examination of Subgroups

No subgroup analyses will be performed for this study. however, subgroup analysis may be conducted as post Hoc analysis.

8. Output Presentations

Appendix 1 shows conventions for presentation of data in outputs.
The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics. Few tables will contain two set of population counts (N1 and N2) for DKP.TRIS/TRAM.HCl and TRAM.HCl each, since placebo subjects will receive either DKP.TRIS/TRAM.HCl or TRAM.HCl after the single dose phase. Thus, N1 and N2 will represent the number of patients under DKP.TRIS/TRAM.HCl and TRAM.HCl arm at the single dose phase and multiple dose phase respectively.

9. Disposition and Withdrawals

All patients who provide informed consent will be accounted for in this study.

9.1. Disposition

Patient disposition including count and percentage of patients screened, screen failures, randomized, completed the treatment, discontinued the study, reason for discontinuation of treatment, completed the study, discontinued the study, and reason for discontinuation of study will be tabulated by treatment group and overall.
Completion and discontinuation of study treatment can be identified from the filed “Date of Treatment discontinuation” of eCRF page “End of study”. If the date is missing then the patient

completed the treatment, and if the date is not missing then patient discontinued the treatment. Completion and discontinuation of study can be identified based on the treatment discontinuation date and study completion or discontinuation date.

- If both the dates are same, then the patient discontinued the study.
- If the dates are different and the difference between the study completion/ discontinuation date and the screening date is at least 6, then the patient is completed the study else discontinued.

Number and percentage of patients in each population and exclusion patients from each population will also be summarized. Percentages for population exclusion will be based on ITT population.

Patients who are excluded from safety, ITT, mITT and PP population and reason for exclusion from PP population will be listed.

9.2. PROTOCOL DEVIATIONS

All PDs will be recorded and classified in Clinical Trial Management System (CTMS).

All protocol deviations (PD) will be discussed and reviewed on a case-by-case basis before the DBL. Additional evaluation regarding the COVID-19 related PDs will be implemented and discussed before the DBL. In acknowledgement of multiple regulatory guidance (FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic, FDA, 2020; Guidance on the Management of Clinical Trials during the COVID-19 Pandemic, EMA, 2020; Points to consider on implications of Coronavirus disease on methodological aspects of ongoing clinical trials, EMA, 2020) protocol deviations due to COVID-19 pandemic will be summarized and will be indicated in the listing of protocol deviation.
All PDs authorized by Sponsor will be documented.

Individual PDs will be presented in a data listing. The number and percentage of patients with major/critical PDs as well as the number and percentage of patients with major/critical PDs that could affect the primary efficacy analysis will be summarized by deviation on ITT population. Additional Major and Minor PDs may be identified during data review and will be reflected in the Table and Listing as appropriate.
All PDs will be recorded and classified in Clinical Trial Management System (CTMS).

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ITT and mITT.
No statistical testing will be carried out for demographic or other baseline characteristics.
The following demographic and other baseline characteristics will be reported for this study.

- Age (years)
- Sex
- Childbearing potential for female subjects
- Race
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Baseline radiculopathy categories
- NRS-PI score at baseline
- Baseline PI categories
- Roland Morris Disability Questionnaire Score

10.1. DERIVATIONS

- BMI (kg/ m^2) = weight (kg)/ height (m)^2

11. MEDICAL AND SURGICAL PROCEDURE HISTORY

Medical and Surgical Procedure History information will be presented for the ITT and mITT.

- Medical History data captured on eCRF will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 24.1 or latest) dictionary
    - Medical History conditions are defined as those conditions which stop prior to or at Screening.
    - Presented by SOC and PT.

A listing will be provided for both medical and surgical procedure history.

12. CONCOMITANT ILLNESSES

Concomitant Illnesses will be presented for the SAF.

- Concomitant Illnesses will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 24.1 or latest available) dictionary
    - Concomitant Illnesses are conditions started prior to or at Screening and are ongoing at the date of Screening.
    - Presented by SOC and PT.
    - Concomitant illness conditions are defined as those conditions recorded in the eCRF form "Medical History".

13. PRIOR, CONCOMITANT AND POST TREATMENT MEDICATIONS/ NON-DRUG TREATMENT

Medications will be presented for the SAF and coded using WHO Drug dictionary Version 01SEP2021 or latest available. See Appendix 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case, i.e. concomitant.
Frequency tabulations will be presented for prior and concomitant medications by preferred name.

- 'Prior' medications are medications which started and stopped prior to the first dose of study medication.
- 'Concomitant' medications are medications which:
    - started prior to, on or after the first dose of study medication,
    - AND ended on or after the date of first dose of study medication or were ongoing at the end of the study.

Concomitant medications will be summarized separately for single dose and multiple dose phases. Concomitant medications which are stopped prior to first multiple dose start date will be summarized for single dose phase. Concomitant medications that are failed to include in single dose phase will be summarized for multiple dose phase.
Concomitant medications ending on the multiple dose phase start date/time will be considered for the multiple dose phase summary, unless the end time of the medication is known to be prior to the multiple dose phase.

- "Post Treatment" medications are medications which are started after the multiple dose end date.

A listing of concomitant non-drug treatment will be provided for SAF.

13.1. RESCUE MEDICATION

Summary of rescue medication will be presented for ITT and mITT separately for single dose phase and multiple dose phase. The summary will include the number of subjects took rescue medication, the frequency of rescue medication (1 time, 2 times, 3 times, and more than 3 times), summary of NRS PI score before taking rescue medication, frequency of NRS PI score before rescue medication, frequency of VRS-PAR score before taking rescue medication.

A listing of RM t will be provided for ITT.

14. STUDY MEDICATION EXPOSURE

Exposure to study medication in hours will be presented for the SAF.
The extent of exposure will be calculated for DKP.TRIS/TRAM.HCl and TRAM.HCl. Exposure to placebo will not be summarized since it is administered only at one time and interruptions, dose change, and noncompliance are not applicable for placebo as per the study design.

Exposure will be calculated separately for patients received DKP.TRIS/TRAM.HCl or TRAM.HCl at t0 and patients switched to DKP.TRIS/TRAM.HCl or TRAM.HCl in the multiple dose phase.
The date and time of first study medication administration will be taken from the eCRF "Study drug administration at t0h" form. The date and time of first study medication for the multiple dose phase (t8) will be taken from the e-diary data. The date of last study medication will be taken from the eCRF "End of Study" form. In the case of missing data on the eCRF, the e-diary data will be used in order to determine the first and last date of study medication.
Interruptions, compliance, and dose changes are not considered for duration of exposure.

14.1. DERIVATIONS

Duration of exposure of study medication (minutes),

- For patients received DKP.TRIS/TRAM.HCl or TRAM.HCl at t0 = (Date/Time of last study medication administration – Date/Time of first study medication administration (t0))/60.
- For patients switched to DKP.TRIS/TRAM.HCl or TRAM.HCl in the multiple phase = (Date/Time of last study medication administration – Date/Time of first study medication administration on multiple phase (t8))/60.

15. STUDY MEDICATION COMPLIANCE

Compliance to study drug will be presented for the SAF population.

A table consisting of summary statistics for percent compliance along with the number and percent of patients with compliance in each of the following groups: <80%, =>80% - <=120% and >120% as well as the overall number and percentage of patients compliant for each treatment group and overall will be produced by phases and across the whole study on SAF population.

A listing of drug accountability will be presented on SAF population to account for all drug distributed to each patient, including the box number, total number capsules dispensed, returned, consumed, lost (if any). percentage compliance and compliant (yes/no) will also be displayed for study drug.

15.1. DERIVATIONS

Compliance with study drug based on the drug accountability data will be calculated as the number of capsules/tablets taken x 100 / expected number of tablets/capsules which should have been taken expressed as a percentage, see calculations below.

$$\text{Compliance}(\%) = \frac{\text{units of tablets/capsules actually taken}}{\text{Total units of tablets / capsules expected to be taken}} \times 100$$

The actual number of tablets/capsules taken can be identified from the drug accountability data collected in the eCRF. The "Amount Consumed" field in the "Drug Return and Accountability" page of eCRF will provide the number of tablets/capsules consumed by each patient. The expected number of total tablets/capsules taken for each patient will be 39 based on 13 (thirteen) administrations with 1 tablet and 2 capsules per administration. For patients who permanently stop the study medication, the expected number of tablets/capsules will be calculated up-to the date of study withdrawal.

16. EFFICACY OUTCOMES

16.1. PRIMARY EFFICACY

16.1.1. PRIMARY EFFICACY VARIABLE(S) & DERIVATION(S)

The primary efficacy variable is time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose.
The time to achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% will be the minimum of the following 2 values,

1) The time (till 8 hours after the first dose) where a patient achieves an NRS-PI score <4.
2) The time (till 8 hours after the first dose) where a patient is achieving a percentage change in PI score from baseline ≤ -30%.

16.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE(S)

Handling of missing data need to follow as per section 7.3

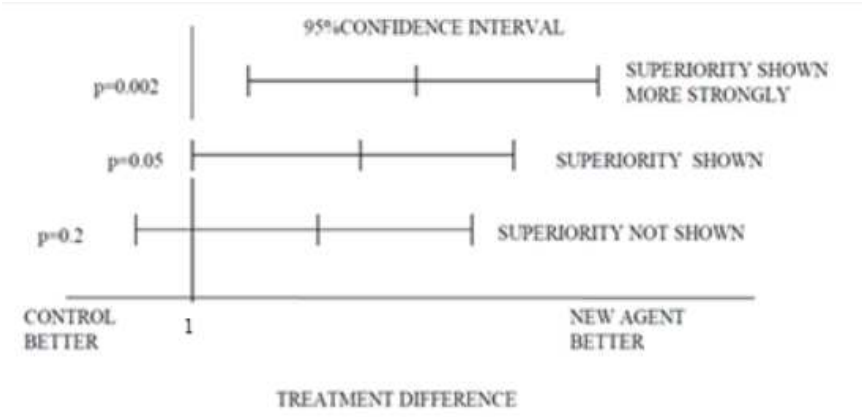
16.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)

The primary objective of this study is to evaluate the analgesic efficacy of DKP.TRIS/TRAM.HCl versus placebo by the time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose.

The primary efficacy analysis will be performed for the mITT population, where the randomization scheme 4:4:1:1 is properly respected. The ITT population (total cohort of patients randomized) will be used to assess the robustness of the results obtained using the mITT population. The results of mITT and ITT analyses will be compared, and the two analyses will be concordant if both reach the same conclusions.

The analysis will be performed for the superiority of DKP.TRIS/TRAM.HCl versus placebo using a Cox Proportional Hazard (CPH) model with treatment, baseline PI categories and baseline radiculopathy categories as covariates/ factors.
Hazard ratio ((DKP.TRIS/TRAM.HCl)/ Placebo) will be presented together with two-sided 95% CI and p-value for the test for significance of the difference at 5% significance level.

Figure 2: Hypotheses for Superiority Test



The Hypothesis to be tested is;

H_0: HR = 1

Vs

H_1: HR ≠ 1

Where HR is hazard ratio comparing DKP.TRIS/TRAM.HCl to Placebo.
If the lower confidence interval for the Hazard Ratio is greater than 1, the superiority is achieved.

In case of proportional hazard assumption is not satisfied, covariates with nonproportional effects may be incorporated into the model as stratification factors rather than predictors. Assumption of Proportionality will be examined based on supremum test using PROC PHREG SAS procedure.

Table 1

Situation	Censoring/Event Rule
NRS-PI score <4 or a pain intensity reduction of ≥30% at timepoint t_i without prior Rescue Medication	Event at t_i
Completed study without achieving NRS-PI score <4 or a pain intensity reduction of ≥30%	Censor at timepoint of 8 hours

The NRS-PI Score is obtained from Diary Data (NRS-PI).
The NRS-PI Score will be summarized categorically based on the following categories: 0, 1, 2, 3, and >=4.

If the NRS PI at 8th hour is captured after 15 minutes from the second dose, then those PI values will not be included in the analysis, since the maximum plasma concentration (Cmax) is reaching at 30 minutes (ranging from 15 to 60 minutes) when DKP.TRIS is orally administered in humans. Also, the analgesic effect of DKP starts after 15 minutes.

16.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)

16.1.4.1. Intent-to-Treat Analysis

Primary efficacy endpoints will be analyzed using the ITT population.

16.1.4.2. Per protocol Analysis

Primary efficacy endpoints will be analyzed using the PP population.

16.1.4.3. No Data Imputation

Analysis will be carried out on primary endpoint without any imputation on missing values regardless of whether or not the rescue medication is taken on mITT, ITT, and PP population. Only observed values will be used for the analysis.

Table 2

Situation	Censoring/Event Rule
NRS-PI score <4 or a pain intensity reduction of ≥30% at timepoint t_i without prior Rescue Medication	Event at t_i
Completed study without achieving NRS-PI score <4 or a pain intensity reduction of ≥30%	Censor at timepoint of 8 hours
Early Discontinuation	Censor at Time of Last Assessment
Early Discontinuation and later known to have a death	Censor at Time of Last Assessment
Intake of Rescue Medication before event/without event	Censor at Time of Rescue Medication

16.1.4.4. Multiple Imputation

An analysis based on the envisage in which the intake of RM would not occur. This will be analyzed using MI based on the missing data assumption Missing at Random (MAR) on mITT, ITT, and PP population. This process will follow five steps:

1) Consider the values collected for the 6 hours after the RM intake as missing.
2) Partially impute the data for a monotone missing pattern with 100 as a number of imputations and "1234" as seed number. Employ the Markov Chain Monte Carlo (MCMC) method with treatment, baseline PI categories, baseline radiculopathy, and Baseline Roland Morris Disability Questionnaire score
3) Impute the monotone data using a regression imputation model. Apply by imputation using seed number "1234" with treatment, baseline PI categories, baseline radiculopathy, and Baseline Roland Morris Disability Questionnaire score
4) Each multiple imputed dataset in Step 3 will be analyzed separately, as described in Section 16.1.3 of the SAP.
5) The estimates (LS means, CI, etc.) from the model analysis in Step 4 will be combined using Rubin's combination rules for statistical inference

Refer Table 1 for censoring/event rules.

Refer Appendix 1 for more details.

16.1.4.5. Inclusion of strata variables collected in the CRF instead of IRT strata variables

Primary efficacy endpoints will be analyzed on mITT, ITT, and PP population by replacing the strata variables (baseline NRS PI categories and baseline radiculopathy categories) collected in the IRT by the strata variables derived/collected based on the CRF data.
Screening NRS PI will be classified into two groups based on the score collected at screening as follows.

- Moderate pain: if the Screening NRS PI is between 5 and 7 (both inclusive)
- Severe pain: if the screening NRS PI is >7

Baseline radiculopathy categories are collected in the "Quebec Task force classification" page in the CRF at screening visit. The categories to be considered are,

- LBP without radiation
- LBP+ radiation to extremity, proximally

- LBP+ radiation to extremity, distally

If the sensitivity analysis will show that the mITT, ITT, and PP primary endpoint result and conclusions are not affected by the incorrect stratification on randomization, the ITT and PP results can be regarded as certainty. If sensitivity analyses will identify that the incorrect stratification on randomization influences the ITT and PP primary endpoint results, additional subgroups analysis will be performed to try to resolve these inconsistencies. If this cannot be achieved, the impact of the incorrect stratification on the primary endpoint results will be interpreted and justified in the Clinical Study Report.

16.1.4.6. Removal of patients with incorrect stratification on randomization

Primary efficacy endpoints will be analyzed on mITT, ITT, and PP population by removing the patients with incorrect stratification at screening. i.e., the patients who are having difference in stratification categories (baseline NRS PI categories and baseline radiculopathy categories) between CRF and IRT will be omitted from the analysis.

16.2. SECONDARY EFFICACY

The secondary efficacy analyses will be performed for the PP population, mITT population, and ITT population.
These includes:

Single-dose phase

- Pain Relief (PAR) scores at each prespecified time point (t15m, t30m, t1h, t1.5h, t2h, t4h, t6h, t8h) over the 8 hours after the first dose
- TOTPAR at 4, 6, and 8 hours (TOTPAR4, TOTPAR6, TOTPAR8) after the first dose
- Percentage of maximum TOTPAR (% max TOTPAR) at 4, 6, and 8 hours after the first dose
- Percentage of patients achieving at least 50% of maximum TOTPAR at 4, 6, and 8 hours after the first dose
- Pain Intensity (PI) scores at each prespecified time point (t15m, t30m, t1h, t1.5h, t2h, t4h, t6h, t8h) over the 8 hours after the first dose
- SPID at 4, 6, and 8 hours (SPID4, SPID6, SPID8) after the first dose
- Percentage of maximum SPID (% max SPID) at 4, 6, and 8 hours after the first dose
- Percentage of patients achieving at least 30% of PI reduction versus baseline at 4, 6, and 8 hours after the first dose
- PGE of the study medication at 8 hours after the first dose

- Time to RM (Minutes): Time elapsed between treatment administration and the first dose of RM from baseline till 8 hours after the first dose
- Percentage of patients who required RM within the first 4, 6, or 8 hours post-dose.

Multiple-dose phase

- Pain Relief (PAR) scores at each prespecified time point
- TOTPAR at 24, 48, 72, and 96 hours (TOTPAR24, TOTPAR48, TOTPAR72, TOTPAR96).
- Percentage of maximum TOTPAR (% max TOTPAR) at 24, 48, 72, and 96 hours of the multiple-dose phase.
- Percentage of patients achieving at least 50% of maximum TOTPAR at 24, 48, 72, and 96 hours of the multiple-dose phase.
- Pain Intensity (PI) scores at each prespecified time point over the multiple-dose phase.
- SPID at 24, 48, 72, and 96 hours (SPID24, SPID48, SPID72, SPID96) of the multiple-dose phase.
- Percentage of maximum SPID (% max SPID) at 24, 48, 72, and 96 hours of the multiple-dose phase.
- Percentage of patients achieving at least 30% of PI reduction versus baseline at 24, 48, 72, and 96 hours of the multiple-dose phase.
- PGE at 96 hours of the multiple-dose phase.
- Percentage of patients who required RM within 24, 48, 72, and 96 hours of the multiple-dose phase.
- Roland Morris Disability Questionnaire at 96 hours of the multiple-dose phase.
- Treatment Satisfaction Questionnaire for Medication at 96 hours of the multiple-dose phase

Complete treatment and assessment period (single and multiple-dose phase combined)

- Time to first achieve an NRS score <4 or a pain intensity reduction $\geq 30\%$ from the first drug intake till 5 days post-treatment, excluding patients assigned to placebo treatment arm during the single dose phase.
- TOTPAR over 104 hours from the first drug intake till 5 days post-treatment (TOTPAR104), excluding patients assigned to placebo treatment arm during the single dose phase.
- SPID over 104 hours from the first drug intake till 5 days post-treatment (SPID104), excluding patients assigned to placebo treatment arm during the single dose phase.
- Time to RM: Time elapsed between the first drug intake till 5 days post-treatment, excluding patients assigned to placebo treatment arm during the single dose phase.

The assessments performed after 15 minutes from the second dose at 8th hour will not be considered

for the single dose phase analysis, but for multiple dose phase.
Multiple dose phase analysis will include only those assessments which are collected after the date and time of second dose of study medication. i.e., if a subject skipped the second dose at 8th hour and took the dose at 16th hour, then those assessments performed after the 16th hour will be considered for the analysis. In this case, assessments performed at t10h and t16h (if the assessment at t16h is before the time of second medication + 15 minutes) will be omitted.

16.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

16.2.1.1. Total Pain Relief (TOTPAR)

TOTPAR is calculated as the time-weighted sum of the PAR-VRS scores.
The general formula for calculating TOTPARx is as follows:
TOTPAR4 = ∑ [T(i) – T(i-1)] x PAR(i) for i = 15m, 30m, 1h, 1.5h, 2h, 4h
TOTPAR6 = ∑ [T(i) – T(i-1)] x PAR(i) for i = 15m, 30m, 1h, 1.5h, 2h, 4h, 6h
TOTPAR8 = ∑ [T(i) – T(i-1)] x PAR(i) for i = 15m, 30m, 1h, 1.5h, 2h, 4h, 6h, 8h
TOTPAR24 = ∑ [T(i) – T(i-1)] x PAR(i) for i = from 10h to 32h
TOTPAR48 = ∑ [T(i) – T(i-1)] x PAR(i) for i = from 10h to 56h
TOTPAR72 = ∑ [T(i) – T(i-1)] x PAR(i) for i = from 10h to 80h
TOTPAR96 = ∑ [T(i) – T(i-1)] x PAR(i) for i = from 10h to 104h
TOTPAR104 = ∑ [T(i) – T(i-1)] x PAR(i) for i = 15m, 30m, 1h, 1.5h, 2h, 4h, 6h, 8h, 10h, …, 104h
where T(i) is the scheduled time, T(0) = 0, PAR(i) = PAR at time i.

Please note that starting from multiple phase values are collected before and two hours after each intake and that for the evaluation of TOTPAR104 patients taking Placebo during the single phase will be excluded.

16.2.1.2. Percent (%) max TOTPAR

The max TOTPAR is calculated as the theoretical maximum time-weighted sum of the PAR values for each patient. The maximum possible TOTPAR is the value of TOTPAR that would be obtained if the patient has a complete pain relief for that observation period (i.e., PAR at each post-baseline time point evaluated was 4).
The general formula for calculating max TOTPARx is as follows:
max TOTPAR4 = ∑ [T(i) – T(i-1)] x 4 for i = 15m, 30m, 1h, 1.5h, 2h, 4h
max TOTPAR6 = ∑ [T(i) – T(i-1)] x 4 for i = 15m, 30m, 1h, 1.5h, 2h, 4h, 6h

max TOTPAR8 = ∑ [T(i) – T(i-1)] x 4 for i = 15m, 30m, 1h, 1.5h, 2h, 4h, 6h, 8h
max TOTPAR24 = ∑ [T(i) – T(i-1)] x 4 for i = from 10h to 32h
max TOTPAR48 = ∑ [T(i) – T(i-1)] x 4 for i = from 10h to 56h
max TOTPAR72 = ∑ [T(i) – T(i-1)] x 4 for i = from 10h to 80h
max TOTPAR96 = ∑ [T(i) – T(i-1)] x 4 for i = from 10h to 104h
max TOTPAR 104 = ∑ [T(i) – T(i-1)] x 4 for i = 15m, 30m, 1h, 1.5h, 2h, 4h, 6h, 8h, 10h, …, 104h
where T(i) is the scheduled time and T(0) = 0.

The % max TOTPAR is the ratio between the TOTPAR of each patient and its theoretical maximum TOTPAR for a certain observation period.
The general formula for calculating % max TOTPARx is as follows:
% max TOTPAR4 = TOTPAR4/ max TOTPAR4
% max TOTPAR6 = TOTPAR6/ max TOTPAR6
% max TOTPAR8 = TOTPAR8/ max TOTPAR8
% max TOTPAR24 = TOTPAR24/ max TOTPAR24
% max TOTPAR48 = TOTPAR48/ max TOTPAR48
% max TOTPAR72 = TOTPAR72/ max TOTPAR72
% max TOTPAR96 = TOTPAR96/ max TOTPAR96

16.2.1.3. % max TOTPAR104 = TOTPAR104/ max TOTPAR104Summed Pain Intensity Difference (SPID)

SPID is calculated as the time-weighted sum of the pain intensity difference (PID) values, where PID is the difference in Pain Intensity calculated at each timepoint respect to the baseline value.
The general formula for calculating SPIDx is as follows:
SPID4 = ∑ [T(i) – T(i-1)] x PID(i) for i = 15m, 30m, 1h, 1.5h, 2h, 4h
SPID6 = ∑ [T(i) – T(i-1)] x PID(i) for i = 15m, 30m, 1h, 1.5h, 2h, 4h, 6h
SPID8 = ∑ [T(i) – T(i-1)] x PID(i) for i = 15m, 30m, 1h, 1.5h, 2h, 4h, 6h, 8h
SPID24 = ∑ [T(i) – T(i-1)] x PID(i) for i = from 10h to 32h
SPID48 = ∑ [T(i) – T(i-1)] x PID(i) for i = from 10h to 56h
SPID72 = ∑ [T(i) – T(i-1)] x PID(i) for i = from 10h to 80h
SPID96 = ∑ [T(i) – T(i-1)] x PID(i) for i = from 10h to 104h
SPID104 = ∑ [T(i) – T(i-1)] x PID(i) for i = 15m, 30m, 1h, 1.5h, 2h, 4h, 6h, 8h, 10h, …, 104h
where T(i) is the scheduled time, T(0) = 0, PID(i) = PID at time i = PI (0) – PI (i).

Please note that starting from multiple phase values are collected before and two hours after each intake and that for the evaluation of SPID104 patients taking Placebo during the single phase will be excluded.

16.2.1.4. Percent (%) max SPID

The max SPID is calculated as the theoretical maximum time-weighted sum of the PID values for each patient. The maximum possible SPID is the value of SPID that would be obtained if the patient were pain free for that observation period (i.e., PI at each post-baseline time point evaluated was 0).

The general formula for calculating max SPIDx is as follows:

max SPID4 = $\sum$ [T(i) – T(i-1)] x PI(0) for i = 15m, 30m, 1h, 1.5h, 2h, 4h
max SPID6 = $\sum$ [T(i) – T(i-1)] x PI(0) for i = 15m, 30m, 1h, 1.5h, 2h, 4h, 6h
max SPID8 = $\sum$ [T(i) – T(i-1)] x PI(0) for i = 15m, 30m, 1h, 1.5h, 2h, 4h, 6h, 8h
max SPID24 = $\sum$ [T(i) – T(i-1)] x PI(0) for i = from 10h to 32h
max SPID48 = $\sum$ [T(i) – T(i-1)] x PI(0) for i = from 10h to 56h
max SPID72 = $\sum$ [T(i) – T(i-1)] x PI(0) for i = from 10h to 80h
max SPID96 = $\sum$ [T(i) – T(i-1)] x PI(0) for i = from 10h to 104h
max SPID104 = $\sum$ [T(i) – T(i-1)] x PI(0) for i = 15m, 30m, 1h, 1.5h, 2h, 4h, 6h, 8h, 10h, …, 104h

where T(i) is the scheduled time, T(0) = 0.

The % max SPID is the ratio between the SPID of each patient and its theoretical maximum SPID for a certain observation period.
The general formula for calculating % max SPIDx is as follows:

% max SPID4 = SPID4/ max SPID4
% max SPID6 = SPID6/ max SPID6
% max SPID8 = SPID8/ max SPID8
% max SPID24 = SPID24/ max SPID24
% max SPID48 = SPID48/ max SPID48
% max SPID72 = SPID72/ maxSPID72
% max SPID96 = SPID96/ max SPID96
% max SPID104 = SPID104/ max SPID104

All the parameters that use the data captured till 8 hours from the dosing start will be considered in the single dose phase. The assessment results that are collected within 8 hours but after 15 minutes from the second dose will not be used to derive the single dose phase parameters. For example, if a patient has pain relief (PAR) score at 8 hour after 15 minutes of second dose, then the PAR at t8 will

not be used to derive TOTPAR8. In such cases TOTPAR6 and TOTPAR8 will be same for that patient.

16.2.2. Missing Data Methods for Secondary Efficacy Variable(s)

Handling of missing data need to follow as per section 7.3

16.2.3. Analysis of Secondary Efficacy Variables

16.2.3.1. PI-NRS, SPIDs, %max SPIDs, TOTPARs, %max TOTPARs and Roland Morris Disability Questionnaire (RMQ)

A descriptive statistical summary will be provided for each of the endpoints. Additionally, these endpoints will be analysed using Analysis of Covariance (ANCOVA). For all the endpoints except RMQ will be analysed considering treatment and the baseline PI-NRS as covariates.
RMQ will be analysed with Treatment and baseline RMQ score as covariates.

LS means will be presented for each of the treatment groups. In addition, estimates of the treatment effect will be presented together with a one sided 95% CI for the difference and p-value for the test for significance of difference at 5% significance level.

Additionally, percent improvement from Baseline in the Roland Morris Disability Questionnaire score will also be presented by treatment. Patients assigned to placebo treatment arm during the single dose phase will be excluded. Roland Morris Disability Questionnaire score is calculated from each fully completed questionnaire using proportional recalculation method. For example, if 17 questions had been answered "Yes," a raw sum score of 17 would be a proportional recalculated score of 71% if all 24 questions were answered (17/24 × 100). However, the raw sum score of 17 would be proportionally recalculated to a score of 81% if 3 questions had not been answered (17/(24–3) × 100).

The below given endpoints with binary outcomes will be analysed using chi-square test at 5% significance level. Odds ratio will be presented together with a two-sided 95% CI for the difference and p-value for the test for significance of difference. An additional Cochran–Mantel–Haenszel (CMH) test will be performed by adjusting the covariates baseline PI categories and baseline radiculopathy categories. Odds ratio will be presented with two-sided 95% CI and p-value.

- Percentage of patients achieving at least 50% of maximum TOTPAR at 4, 6, and 8 hours after the first dose

- Percentage of patients achieving at least 30% of PI reduction versus baseline at 4, 6, and 8 hours after the first dose
- Percentage of patients achieving at least 50% of maximum TOTPAR at 24, 48, 72, and 96 hours of the multiple-dose phase
- Percentage of patients achieving at least 30% of PI reduction versus baseline at 24, 48, 72, and 96 hours of the multiple-dose phase
- Percentage of patients who required RM within the first 4, 6, or 8 hours post-dose
- Percentage of patients who required RM within 24, 48, 72, and 96 hours of the multiple-dose phase.

16.2.3.2. PGE and PAR-VRS

PGE (8h after the first dose, and at 96 hours of the multiple dose-phase) and PAR-VRS (at each time point separately) (ordinal variables) will be analysed by Wilcoxon rank-sum test, that is a nonparametric test with the null hypothesis that the probability of an observation from the treatment X exceeding an observation from the second treatment Y is equal to the probability of an observation from Y exceeding an observation from X, against the alternative hypothesis that these probabilities are different.
In an easy way the set of hypotheses can be summarized saying that under H0 the distributions of both treatment populations are equal against the alternative hypothesis that they are not.

16.2.3.3. Time to first use of RM

The time to RM is defined as the time elapsed between treatment administration and RM intake. The formula for calculating time to RM is:

Time to RM (Minutes) = $t_{rm} - t_0$, t_{rm} is the time (hours and minutes) of RM intake
t_0 is the time (hours and minutes) of study drug intake

In the case of no rescue medication intake, time to RM will be calculated as the time that occurred between t_0 and the end of the time period of interest (8 hours after t_0) and the relative patient will be considered as censored.

Time to first use of RM will be assessed using Log-rank test.
An additional CPH model will be performed with treatment, baseline PI categories and baseline radiculopathy categories as covariates/factors.

Hazard ratio ((DKP.TRIS/TRAM.HCl)/ TRAM.HCl) will be presented together with two-sided 95% CI and p-value for the test for significance of the difference at 5% significance level.

Situation	Censoring/Event Rule
RM Intake at t_i	Event at t_i
Completed study without RM Intake	Censor at timepoint of 8 hours

16.2.3.4. Other Analysis

A descriptive summary will be provided for the following endpoints,

- Treatment Satisfaction Questionnaire for Medication at 96 hours of the multiple-dose phase
- Time to first achieve an NRS score <4 or a pain intensity reduction ≥30% from the first drug intake till 5 days post-treatment, excluding patients assigned to placebo treatment arm during the single dose phase.
- TOTPAR over 104 hours from the first drug intake till 5 days post-treatment (TOTPAR104), excluding patients assigned to placebo treatment arm during the single dose phase.
- SPID over 104 hours from the first drug intake till 5 days post-treatment (SPID104), excluding patients assigned to placebo treatment arm during the single dose phase.
- Time to RM (Minutes): Time elapsed between the first drug intake till 5 days post-treatment, excluding patients assigned to placebo treatment arm during the single dose phase. Censoring/Event rule is as follows:

Situation	Censoring/Event Rule
RM Intake at t_i	Event at t_i
Completed study without RM Intake	Censor at timepoint of 5 Days Post-Treatment
Death	Censor at Time of Death
Early Discontinuation without taking RM	Censor at Time of Discontinuation
Early Discontinuation and later known to have a death	Censor at Time of Discontinuation

Non-inferiority of DKP.TRIS/TRAM.HCl versus TRAM.HCl will be tested with a one-sided significance level of 2.5%. Non-inferiority will be satisfied if the lower limit of the confidence interval is greater than a non-inferiority margin:

- For Time to "event" variables, the non-inferiority margin will be 0.80, based on Hazard Ratio.
- For continuous variables the non-inferiority margin will be 20% (0.20), based on the LS Mean

of treatment difference.
- For binary variables the non-inferiority margin will be 0.80, based on the Odds Ratio.

In case the non-inferiority is confirmed on PP population, the superiority of DKP.TRIS/TRAM.HCl versus TRAM.HCl will be also tested on mITT and ITT for all secondary endpoints. All the secondary endpoints related to the single phase will be also analysed for the superiority of DKP.TRIS/TRAM.HCl versus placebo. Non-inferiority will be tested on the PP population and in addition for the secondary endpoints of primary interest (TOPAR24, TOTPAR48) also on the mITT and ITT population. Superiority will only be tested on the mITT and ITT population, if non-inferiority is confirmed on the PP population. For continuous variables, superiority is achieved if the lower confidence interval for the LS Mean of treatment difference is greater than 0. For binary variables, if the lower confidence interval for the Odds ratio/Hazard ratio is greater than 1, then the superiority is achieved.

16.3. EXPLORATORY EFFICACY

16.3.1. EXPLORATORY EFFICACY VARIABLES & DERIVATIONS

The exploratory efficacy variable is the Time to first achieve an NRS-PI score <4 and a pain intensity reduction ≥30% from drug intake till 8 hours post-treatment (single dose phase only)

16.3.2. MISSING DATA METHODS FOR EXPLORATORY EFFICACY VARIABLE(S)

No imputation will be performed for exploratory analysis

16.3.3. ANALYSIS OF EXPLORATORY EFFICACY VARIABLES

Follow the analysis of primary efficacy variable, section 16.1.3. Exploratory analysis will be performed on mITT, ITT, and PP population.

17. QUALITY OF LIFE ANALYSIS

Not Applicable

18. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set.
There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

18.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 24.1 or latest.
Treatment emergent adverse events (TEAEs) are defined as AEs that occurred or worsened in severity after the first administration of study treatment including follow-up [period between the last drug intake and the visit 2].

See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case, i.e. treatment emergent.

An overall summary of number of patients within each of the categories described in the sub-section below, will be provided as specified in the templates.
Treatment emergent AEs will be summarized separately for single dose and multiple dose phases. All TEAEs which are started before the multiple dose phase will be summarized for single dose phase and those TEAEs started on or after the multiple dose phase will be summarized for multiple dose phase.
TEAEs commencing on the multiple dose phase start date/time will be considered for the multiple dose phase summary, unless the start time of the TEAE is known to be prior to the multiple dose phase.
Listings will include TEAEs and Non-TEAEs.

18.1.1. ALL TEAES

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and broken down further by maximum severity and relationship to study medication.

18.1.1.1. Severity

Severity is classed as mild/ moderate/ severe (increasing severity). TEAEs starting after the first

dose of study medication with a missing severity will be classified as severe. If a patient reports a TEAE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

18.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as "Unrelated", "Related" (increasing severity of relationship). A "Related" TEAE is defined as a TEAE with a relationship to study medication as "Certainly Related", "Probable Related", "Possibly Related" or "Un-assessable" to study medication. TEAEs with a missing relationship to study medication will be regarded as "Probably Related" to study medication. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries.

18.1.2. TEAEs Leading to Discontinuation of Study Medication

Treatment-emergent Adverse Events leading to discontinuation of study medication are those events recorded as 'Drug Withdrawal' for the 'Actions taken with study drug treatment' filed on the AE page of the eCRF.
For TEAEs leading to discontinuation of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

18.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the (e)CRF. A summary of serious TEAEs by SOC and PT will be prepared.

18.1.4. Adverse Events Leading to Death

TEAEs leading to Death are those events which are recorded as "Fatal" on the Adverse Events page of the (e)CRF. A summary of TEAEs leading to death by SOC and PT will be prepared.

18.2. Laboratory Evaluations

Results from the central laboratory will be included in the reporting of this study for Hematology, Serum Chemistry, Coagulation test (only at Screening), Pregnancy test and Urinalysis. A list of

laboratory assessments to be included in the outputs is included in the protocol, Section 10.2.

The following summaries will be provided for chemistry, hematology, and Urinalysis data:

- Actual and change from baseline by visit (for quantitative measurements)
- Incidence of clinically significant abnormalities by visit
- Shift from baseline according to normal range criteria (for quantitative measurements and categorical measurements)

A by-patient listing of all laboratory data and pregnancy test data will be presented.

18.2.1. Laboratory Reference Ranges

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

18.3. Vital Signs

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (bpm)
- Height (at Screening only)
- Weight (at Screening only)

Summary statistics for the absolute and change from baseline will be provided. Clinically significant abnormal findings in vital signs will be listed by treatment.

18.4. Physical Examination

The following Physical Examination measurements will be reported for this study as collected on the Physical Examination (PE) eCRF unless otherwise specified below:

- General Appearance

- Head eyes ears and nose
- Mouth teeth and throat
- Neck and thyroid
- Chest
- Heart
- Abdomen
- Dermatologic
- Musculoskeletal
- Circulatory
- Neurologic
- Lymphatic
- Other system examined

The listing of patients with clinically significant abnormal findings will be provided for physical examination data.

19. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Comments

These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

20. REFERENCES

Dobson, A. J. (2002). *An introduction to generalized linear models, 2nd ed.* Chapman & Hall/CRC.

EMA. (n.d.). *Guideline on Missing Data in Confirmatory Clinical Trials*. Retrieved December 15, 2011, from European Medicines Agency: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf

Little, R., & Yau, L. (1996). Intent-to-Treat Analysis for Longitudinal Studies with Drop-Outs. *Biometrics* , vol 52, 1324-1333.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA OUTPUT CONVENTIONS

Outputs will be presented according to the following Global Bios > Processes > GBIOS Processes - Implementation Guidelines and Templates > General Guidelines and Templates > Output Conventions.

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in the given order:

Treatment Group	For Tables, Listings and Graphs
DKP.TRIS 25mg/TRAM. HCl 75 mg	DKP.TRIS/TRAM.HCl
TRAM.HCl 100 mg	TRAM.HCl
Placebo	Placebo Or Placebo-DKP.TRIS/TRAM.HCl Or Placebo-TRAM.HCl

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Time 0	t0

Long Name (default)	Short Name
Time 15 minutes	t15m
Time 30 minutes	t30m
Time 1 hour	t1h
…	
Time 8 hours	t8h
Time 16 hours	t16h
…	…
End of Study Visit	EOS

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Randomized treatment group (or treatment received if it's a safety output), first by active dose [by ascending dose group] and then control/ placebo
- Center-patient ID,
- Date (where applicable),
- For listings where non-randomized patients are included, these will appear in a category after the randomized treatment groups labeled 'Not Randomized'.

TEXT CASE

- For titles and column labels, capitalize important words, i.e. nouns, pronouns, verbs, adverbs and adjectives, but not articles, conjunctions or prepositions.
- All Footnotes will be in sentence case format.
- All symbols used in body of outputs will be footnoted.
- For Continuous Variables the following statistics will be presented on the original scale:
  - Number ("n")
  - Mean
  - Standard Deviation ("SD")
  - Median
  - Minimum ("min")
  - Maximum ("max")
- For Categorical Variables, for each category, the following statistics will be shown in a summary presentation:

- Number ("n")
- Percentage (%)

The percentage of patients in each category relative to the total number of patients in the relevant analysis population will be the default. Percentages relative to the total number of patients in the relevant analysis population with a non-missing assessment will be specified in a programming note on the shell, if required.

- Derived parameters (e.g. BMI) has to keep the result values with 1 decimal.
- Where percentages are presented, a footnote is added to explain what the denominator of the percentage is, in the form "Percentages are calculated relative to the total number of patients in the safety population" as the first footnote.
- All computed percentages are presented with one decimal place but 100% value, where no decimal places are presented.
- Mean and median: 1 more than the number of decimal places allotted in the raw data received from data management.
- SD: 2 more than the number of decimal places allotted in the raw data.
- Minimum and maximum: equal to the number of decimal places allotted in the raw data.
- 95% CI: As for the mean percentages: will be reported to 1 decimal place.
- Percentage is not presented for zero counts.
- Statistical estimates (i.e. LS mean, Hazard ratio) will be reported in 2 decimal
- P values will be reported in 3 decimal places. If p value is less than 0.001, display as "<0.001"

- REFERENCE CODE
  - Primary Analysis of Primary Efficacy Variable(s)

```
Ods output ParameterEstimates=est;
proc phreg data=dataset_name;
    class treatment;
    model AVAL * CENSOR (1) = treatment baseline_PI_categories
    baseline_radiculopathy_categories/ rl=wald alpha=0.05 ties=exact;
    hazardratio trt;
run;
```

  - Missing Data Methods for Primary Analysis of the Primary Efficacy Variable Using Multiple Imputation – Sensitivity Analysis 2

a. Creation of monotone missing data structure:

Intermediate (non-monotone) missing data (since some patients may have missing records in an intermediate timepoint; but then have data for subsequent assessment) will be multiply imputed using Markov chain Monte Carlo (MCMC) method and assuming MAR and multivariate normality.

The SAS procedure PROC MI with the MCMC option will be used.

```
proc mi data=xxx out=yyy nimpute=200 seed=1234 ;
    var treatment timepoints;
    mcmc chain=single nbiter=200 niter=100 impute=monotone;
run;
```

b. Further Imputations:

The dataset with monotone missing data will be imputed using regression model by considering the stratification factors and respective timepoints.

```
proc mi data=yy out=zz nimpute=1 seed=1234 ;
    var treatment timepoints baseline_PI_categories baseline_radiculopathy_categories
    baseline_Roland_Morris_disability_questionnaire;
    class treatment timepoints baseline_PI_categories baseline_radiculopathy_categories
    baseline_Roland_Morris_disability_questionnaire;
    monotone regression;
run;
```

c. Once imputation is done,

```
Ods output ParameterEstimates=est;
Proc phreg data=zz;
```

```
    class _imputation_ treatment;
    model AVAL * CENSOR (1) = treatment baseline_PI_categories
    baseline_radiculopathy_categories baseline_Roland_Morris_disability_questionnaire/
    rl=wald alpha=0.05 ties=exact;
    hazardratio trt;
run;
```

d. The following SAS code will be used to combine the results:

```
proc mianalyze data=est;
    modeleffects ESTIMATE;
    stderr SE;
run;
```

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study med start date OR Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

Note: Medical history and concomitant illness will follow the same derivations

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

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Project Code (Enter 0 for non-billable projects): YYA36087
IQVIA ID (Login ID): q830354
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Source Envelope:
Document Pages: 61
Signatures: 1
Envelope Originator:
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Initials: 0
Aswin Nair
AutoNav: Enabled
One IMS Way
EnvelopeId Stamping: Disabled
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Signer Events	Signature	Timestamp
Giorigio giorgioreggiardo@cvbf.net Security Level: Email, Account Authentication (Required)	Giorigio Signature Adoption: Pre-selected Style Signature ID: 55ABF8D8-F49E-4652-84E3-30F8AB1E18C8 Using IP Address: 93.32.76.184 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): Approvo il documento	Sent: 7/7/2022 2:42:50 AM Viewed: 7/7/2022 5:05:35 AM Signed: 7/7/2022 5:07:00 AM
Electronic Record and Signature Disclosure: Accepted: 7/7/2022 5:05:35 AM ID: e2241d6f-c0f2-442c-95f0-d60109e79ba5		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	7/7/2022 2:42:50 AM
Certified Delivered	Security Checked	7/7/2022 5:05:35 AM
Signing Complete	Security Checked	7/7/2022 5:07:00 AM

Envelope Summary Events	Status	Timestamps
Completed	Security Checked	7/7/2022 5:07:00 AM

Payment Events	Status	Timestamps

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PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
Mobile Signing:	• Apple iOS 7.0 or above • Android 4.0 or above

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