Statistical Analysis plan

Name	Statistical Analysis Plan for the protocol KSL0117
Version	Final version, 1.0

Study drug	OKITASK® 40 mg
Study code	KSL0117
Title of Study	A multicenter, double blind, randomized, parallel groups study to assess the efficacy and tolerability after single oral administration of Ketoprofen lysine salt 40 mg granules versus Placebo in male and female subjects with acute pain syndrome after removal of molar teeth.
Sponsor	Dompé farmaceutici s.p.a.
CRO	IPHARMA LLC
Data Processing	KeyStat Ltd.

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Version control		
Version	**Change date**	**Reason for change**
Draft, 0.1	26 March 2018	Initial version
Draft, 0.2	06 June 2018	Comments regarding handling of missing data
Final 1.0	17 July 2018	Document finalization

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1. INTRODUCTION

This plan describes a planned statistical analysis for the clinical study protocol number KSL0117 of "Dompé farmaceutici s.p.a.": «*A multicenter, double blind, randomized, parallel groups study to assess the efficacy and tolerability after single oral administration of Ketoprofen lysine salt 40 mg granules versus Placebo in male and female subjects with acute pain syndrome after removal of molar teeth*».

2. LIST OF ABBREVIATIONS

Abbreviation	Explanation
AA	Arachidonic acid
ADME	Absorption, Distribution, Metabolism, Excretion
ADR	Adverse drug reaction
AE	Adverse events
ALAT	Alanine aminotransferase
ALT	Alanine transaminase
AR	Adverse Reaction
ASA	Acetylsalicylic acid
ASAT	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BAA	Biologically Active Additives
BAS	Biologically Active Supplements
BMI	Body mass index
BP	Blood pressure
CFS	Cell-free supernatant
CI	Confidence Interval
CNS	Central nervous system
COX	Cyclo-oxygenase
CPR	Creatine phosphokinase
CRF	Case report form
CVS	Cardiovascular system
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram/electrocardiography
eCRF	Electronic Case Report Form
ED	Early discontinuation (early discontinuation visit)
ET	End of treatment
ETV	Early Termination Visit
EU	European Union
FS	Food Supplement
FVC	Forced vital capacity
GI tract	Gastro-intestinal tract
GLP	Good Laboratory Practice
H	Hour
HR	Heart rate
I.V.	Intravenous
IASP	International Association for the Study of Pain
ICD	International Classification of Disease

Abbreviation	Explanation
ICSRs	Individual case safety report
IEC	Independent Ethics Committee (local)
IMP	Investigational medicinal product
ITT	Intention-to-treat population
KA	Ketoprofen acid
KLS	Ketoprofen lysine salt
KP	Ketoprofen
LME	Liner mixed-effect model
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MoH	Ministry of Health
NSAIDs	Non-steroid anti-inflammatory drugs
NZW	New Zealand White
OA	Osteoarthritis
OTC	Over-the-Counter
PD	Pharmacodynamic(s)
PG	Prostaglandins
PID	Pain intensity different
PK	Pharmacokinetic(s)
POM	Prescription only medications
PP	Population per protocol
PT	Preferred Term
RA	Rheumatoid arthritis
REMD	Rescue medication
RR	Respiration Rate
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SD	Standard deviation
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operation Procedures
TC	Telephone contact
TEAEs	Treatment-Emergent Adverse Events
TESS	Treatment Emergency Signs and Symptoms
TFPR	Time to first perceptible relief
TK	Toxicokinetic
TMPR	Time to meaningful pain relief
ULN	Upper limit of normal
VAS	Visual Analogue Scale
WHO	World Health Organization

3. STUDY DESIGN

This is a multicenter, double-blind, randomized, parallel groups, placebo-controlled study to assess the efficacy and safety of OKITASK® 40 mg granules in patients with acute pain syndrome after removal of molar teeth. The study will be conducted at 3-6 Russian sites. A total expected number of enrolled subjects is 70 (35 per each group). Patients' enrollment to the sites is competitive.

The study will consist of three periods: screening, study treatment and follow-up.

3.1 SCREENING

At Screening after signing the informed consent form, patient's demography, medical history and concomitant medications will be collected, oral cavity will be examined, weight and vital signs will be measured and pregnancy test will be performed for inclusion/exclusion criteria assessment. Screening procedures might take up to 4 days before the scheduled tooth extraction procedure including the actual day of extraction.

On Day 1 the patient will undergo extraction of a molar tooth as indicated for the patient's dental condition. The tooth extraction will be conducted using routine technics and anesthetics (recommended types of anesthesia are provided in section 5.9 Concomitant and rescue therapy of the protocol). After that the patient will stay at the site for treatment of pain syndrome according to the protocol.

Pain intensity will be assessed using VAS within 3 hours after the tooth extraction procedure. Patient's overall assessment will be also recorded. If pain intensity on VAS is above 30 mm and pain relief is required, the patient will be randomized in the study.

3.2 STUDY TREATMENT

The patients will be assigned to one of two treatment group in 1:1 ratio:

- Group 1. OKITASK® 40 mg – 35 patients
- Group 2. Placebo – 35 patients

The patient will assess pain by VAS at 0' – immediately before study drug dosing.

Upon study drug administration the patients will immediately start two stopwatches. One of them will be stopped once the patient feels first perceptible pain relief; the second one will be stopped once the patient feels the meaningful pain relief.

The patient will stay at the site for 6 hours post-dose for pain and AE assessment. Pain intensity will be assessed by VAS at 5', 10', 15', 30', 45', 60' (1 hour), 90' (1.5 hours), 120' (2 hours), 180' (3 hours), 240' (4 hours), 300' (5 hours), and 360' (6 hours) post-dose.

Pain relief will be assessed by VAS at 5', 10', 15', 30', 45', 60' (1 hour), 90' (1.5 hours), 120' (2 hours), 180' (3 hours), 240' (4 hours), 300' (5 hours), and 360' (6 hours) post-dose.

Patients should mark actual time points of VAS measurement. Deviations from planned time points will not be considered as protocol deviations. Only omitted values will be considered as protocol deviations.

Patients' overall assessment will be performed right before the discharge from the site.

Follow-up phone call to the patient to assess AEs will be performed on Day 3 (48 hours

after the study drug dosing). Any SAE spontaneously reported by the patient within 30 days of dosing will be collected.

Should the patient require rescue medication at any time during 6 hours post-dose, the last VAS measurement and patient's overall assessment will be performed before the rescue medication dosing.

3.3 FOLLOW-UP

Follow-up phone call to the patient to assess AEs will be performed on Day 3±1 (48 hours after the study drug dosing). Any SAE spontaneously reported by the patient within 30 days of dosing will be collected.

The study procedures schedule is summarized in Table 3.1.

Table 3.1 Schedule of visits and procedures

Test/Examination	Screening	Study treatments													ED[1]	Follow-up
		Baseline[2] (Pre-dose)	Study drug/placebo administration	Time (Post-dose)												Phone call
Day	Day-4…Day 1	Day 1		Day 1											Day 1	Day 3±1
Hours		0		0.08	0.17	0.25	0.5	0.75	1	1.5	2	3	4	5	6	>1	48
Minutes		0		5	10	15	30	45	60	90	120	180	240	300	360	>60	
Informed consent & screening n° assignment	X																
Demography	X																
Medical history and underlying disease	X																
Oral cavity examination	X																
Height	X																
Weight	X																
Vital signs	X																
Pregnancy test	X																
Extraction of a molar tooth	X (Day 1)																
Pain Intensity Assessment VAS (0-100 mm)[3]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Inclusion/exclusion criteria[4]	X																
Randomization number assignment		X															
Patient's overall assessment (5-point scale)[5]		X													X	X	
Pain Relief Assessment VAS (0-100 mm)				X	X	X	X	X	X	X	X	X	X	X	X	X	
Time to first perceptible relief (TFPR) measured by stopwatch[6]				X													
Time to meaningful pain relief (TMPR) measured by stopwatch[7]				X													
Rescue medication (if applicable)[8]																X[9]	
Concomitant medications	X	X		X												X	X
Previous therapy(ies)	X	X															
Adverse events	X	X		X												X	X

[1] Should the patient require rescue medication at any time during 6 hours post-dose, the last VAS measurement and patient's overall assessment will be performed before the rescue medication dosing. Subjects will be encouraged to postpone the rescue medication until after 1-hour post-dose. The ED assessments will be performed before rescue treatment; actual time of VAS will be captured.

[2] After surgery, before the study drug administration

[3] Patients should mark actual time points of VAS measurement. Deviations from planned time points will not be considered as protocol deviations. Only omitted values will be considered as protocol deviations.

[4] Confirmation of the Inclusion/Exclusion criteria prior to randomization

[5] Patients should mark actual time points of VAS measurement. Deviations from planned time points will not be considered as protocol deviations. Only omitted values will be considered as protocol deviations.

[6] The time of stopwatch will be recorded on eCRF

[7] The time of stopwatch will be recorded on eCRF

[8] Height will be registered as reported by the patient.

[9] In the event of poor pain control, subjects will be allowed access to rescue medication for analgesia (Paracetamol 500-1000 mg). Time to REMD (rescue) with an alternative analgesic, if it occurred, will be recorded. Subject will be encouraged to postpone the rescue medication until after 1 h post dose. If Paracetamol 500-1000 mg is not effective, the patient will be allowed to take another dose of Paracetamol 500-1000 mg every 6-8 hours; maximum daily dose is 4000 mg.

3.4 RANDOMIZATION AND RECEIVING OF THE STUDY DRUG

This is a double-blind placebo-controlled study. Patients will be assigned to one of two treatment groups by the IWRS system in 1:1 ratio:

- Group 1. OKITASK® 40 mg – 35 patients
- Group 2. Placebo – 35 patients

Randomization will be performed after the surgery upon confirmation of the inclusion/exclusion criteria (VAS ≥30 mm). The double-blinding is provided by Placebo that is identical to OKITASK® 40 mg granules.

3.5 BLINDING

The drug will be packaged and labeled in a manner that will exclude unblinding. IWRS will assign the study drug kit number that should be administrated by the subject. Randomization and IWRS manual will be provided to the Investigator before the beginning of the study.

3.6 UNBLINDING

The code of a particular subject may be broken in a medical emergency if knowing the identity of the treatment allocation would influence the treatment of the subject. Administration of rescue therapy does not require code break. Unblinding of a patient's treatment may be performed in IWRS. The reason for breaking the code must be documented in the source documentation. If possible, Medical Monitor should be contacted before the code is broken; otherwise the Medical Monitor should be notified within 24 hours of breaking the code.

4. CONCOMITANT MEDICATION

All concomitant medications, including herbal therapy and biologically active supplements (BAS) must be registered in the source documentation and on the eCRF. This includes all pharmaceutical products and BAS.

The concomitant therapy also includes anesthesia and rescue therapy allowed by the protocol which is applied to relief pain (if applicable).

Ultracain D (articaine 40 mg), Ultracain DS forte (articaine+epinephrine 40 mg+0.01 mg/ml), Ultracain DS (articaine+epinephrine 40 mg+0.005 mg/ml) 1-2 capsules can be used for anesthesia. The Investigator can choose anesthesia taking into consideration the patient's condition, medical history and other reasons. Number of used capsules and type of anesthesia for each patient will be recorded in the source documentation and on the eCRF.

In the event of poor pain control, the patient will receive a rescue medication for analgesia (i.e. Paracetamol 500-1000 mg tablets). Subjects will be encouraged to postpone the rescue medication until after 1-hour post-dose. If Paracetamol 500-1000 mg is not effective, the patient will be allowed to take another dose of Paracetamol 500-1000 mg every 6-8 hours; interval between dose taking is not less than 4 hours; the maximum daily dose is 4000 mg.

The drug name (preferably the name of the active substance), dosage, frequency of administration, route of administration, indication for use (including the underlying disease, comorbid conditions, adverse event, or prevention), the date of beginning and ending of a concomitant drug administration should be registered in the source

documentation and on the electronic Case Report Form.

If by the time of the study completion the concomitant therapy continues, a corresponding mark shall be entered on the electronic Case Report Form.

4.1 PROHIBITED THERAPY

Prohibited medicines which should not be taken within 48 hours before screening and during Day 1:

- Antihistamines;
- Sedating medication (including herbal therapy and BAS).

Prohibited drugs should not be taken during Day 1:

- Medicines for anesthesia other than indicated by the protocol (e.g. procaine, lidocaine);
- NSAIDs and combinations which contain NSAIDs (except for the study drug);
- Analgesics: opioids, acetylsalicylic acid and its derivate, pyrazolones, other analgesics-antipyretics (except for the rescue therapy indicated by the protocol, if applicable);
- Antithrombotic medicines;
- Hemostatic sponge.

Participation in the evaluation of any investigational product within 3 months before screening and during the study is also prohibited.

5. OBJECTIVES OF CLINICAL STUDY

5.1 PRIMARY OBJECTIVES

The primary objective of this study is to assess the efficacy of OKITASK® 40 mg granules versus Placebo in patients with acute pain syndrome after removal of one molar tooth by comparing $AUC_{0\text{-}6h}$ of post-treatment pain profile measured by VAS.

5.2 SECONDARY OBJECTIVES

Secondary objectives of this study are to assess the following efficacy and safety parameters of OKITASK® 40 mg granules versus Placebo in patients with acute pain syndrome after removal of one molar tooth:

- Time profile of pain and time profile of pain relief using VAS scales
- Time to first perceptible pain relief (TFPR) and time to meaningful pain relief (TMPR)
- Proportion of patients requiring rescue medication and time to rescue medication
- Patient's overall assessment
- Rate of adverse events (AE)

6. DETERMINATION OF SAMPLE SIZE[1]

Sample size calculation was based on the paper of Seymour 1996 [3] concerning a randomized, double-blind, placebo-controlled study of treatment with placebo, paracetamol (500 and 1000 mg) and ketoprofen (12.5 and 25 mg).

The unadjusted AUC0-6h values for placebo and ketoprofen were about 263 and 173mmh^{-1}, respectively. The corresponding SD were 106 mm h^{-1} (about 40% of the mean value for placebo AUC) and 121 mmh^{-1} (about 70% of the mean value for ketoprofen 25 mg AUC).

The testing hypothesis for this trial is the superiority of ketoprofen versus placebo that in statistical term is:

H_0: mean of placebo ≥ mean of ketoprofen (no difference between treatments)

H_1: mean of placebo < mean of ketoprofen (clinically and statistically significant difference between the groups) Δ=90 mm h^{-1}

A total of 58 subjects (29 subjects per group) will be necessary to assess a difference of 90 mm h^{-1} between the groups with a power of 80%, α = 0.05, SD=121 mmh^{-1}, and randomization rate of 1:1. Sample size calculation was performed using SAS 9.2[2].

Assuming a drop-out rate of 15%, 70 subjects in total (35 subjects per group) should be enrolled. Considering the screen-failure rate of about 30%, up to 100 patients will be screened in the study.

7. REPLACEMENT OF THE MISSING DATA

7.1 PRIMARY EFFICACY

Considering that the primary variable $AUC_{0\text{-}6h}$ is derived from pain intensity VAS measurements, analyses on primary and secondary variables without or with substitution of missing data, using the last observation carry forward (LOCF) methodology, has been considered in order to avoid bias in the inferential testing of treatment effect.

For LOCF analysis substitution of missing data will be applied only on all patients that have at least one VAS value post-baseline (patient compliant with ITT population definition). Missing post-baseline pain score will be replaced with previous one. **Baseline data (pre-dose) could be carried forward also**. Possibility to use baseline data comes from the data nature, which seems to be linearly decreasing over time. This will allow to calculate AUC in case of missing first post-baseline value (5 minutes).

If data be missing more than one time point after baseline, the data will be qualified as invalid. Consecutive missing values will be replaced with the last non-missing (observed) value. If more than two time points data are missing and after missing data some points have values (non-missing), then all missing sequence will be replaced with last non-missing value. In case of absence non-missing values after two missings, no replacement will be done and data will be find invalid for analysis. Possible cases are presented in table below:

[1] Cite from the Study Protocol
[2] SAS 9.2 http://support.sas.com/documentation/92/

Table 7.1 LOCF missing data replacement cases

Time points	Scale	Scale LOCF	AUC
0 (baseline)	A	A	Valid
1	B	B	
2	.	B	
3	.	B	
4	C	C	
5	D	D	
0 (baseline)	A	A	Valid
1	.	A	
2	B	B	
3	C	C	
4	D	D	
5	E	E	
0 (baseline)	A	A	Invalid
1	.	.	
2	.	.	
3	B	B	
4	C	C	
5	D	D	
0 (baseline)	A	A	Valid
1	B	B	
2	.	B	
3	.	B	
4	.	B	
5	C	C	
0 (baseline)	A	A	Invalid
1	B	B	
2	C	C	
3	.	.	
4	.	.	
5	.	.	

For the sensitivity analysis the fully conditional specification (FCS) regression method[1] will be used for replacing missing data.

SAS code example:

```
proc mi data=pain round=1. seed=13959[2] out=pain_imp;
   class trt;
```

[1] Van Buuren 2007; Brand 1999; Rubin 1987
http://documentation.sas.com/?docsetId=statug&docsetTarget=statug_mi_details07.htm&docsetVersion=14.3&locale=en

[2] Could be any other

```
    fcs nbiter=20 reg (pain=time trt time*trt/details);
    var pain time trt;
run;
```

Pain dataset description:

Alphabetic List of Variables and Attributes						
#	Variable	Type	Len	Format	Informat	Label
4	pain	Num	8	BEST12.	BEST32.	Pain Intensity (VAS)
1	patid	Num	8	BEST12.	BEST32.	Patient ID
5	site	Num	8	BEST12.	BEST32.	Study site
2	time	Num	8	BEST12.	BEST32.	Time (hours)
3	trt	Char	9	$9.	$9.	Therapy

7.2 ADVERSE EVENTS

Treatment emergency sign and symptom (TESS) will be AEs which started after the first study drug dose. Following rules will be applied (Table 7.2):

Table 7.2 TESS classification algorithm

AE start date			Algorithm
Day	Month	Year	
Missed	Missed	Present	If year ≥ year of the first drug dose – TESS
Missed	Missed	Missed	The worst case – TESS
Missed	Present	Missed	The worst case – TESS
Present	Missed	Present	If year ≥ year of the first drug dose – TESS
Missed	Present	Present	If month and year ≥ date of the first study drug dose (month and year) – TESS
Present	Missed	Missed	The worst case – TESS
Present	Present	Missed	The worst case – TESS
Present	Present	Present	Compare dates of AE and the first study drug dose. In case of dates equality qualification will be performed by the sponsor and investigator (questionable TESS)

All questionable TESS flags will be exported to the MS Excel file and send to the sponsor for resolution.

8. ANALYSIS POPULATIONS

Protocol violations/deviation will be defined prior to data-base lock and statistical analysis. Applicability of patient to ITT and PP population will be reviewed by sponsor's medical expert.

8.1 INTENT-TO-TREAT POPULATION

The Intent-to-treat (ITT) population will include all randomized patients who receive at

least one dose of study medication and have at least one post-baseline[1] efficacy measurement; it will be based on the treatment randomized, regardless of the treatment actually received. The ITT will be used for all efficacy analyses. Subject will be summarized according to the treatment to which they were randomized.

8.2 POPULATION PER PROTOCOL

ITT population patients comply with the per-protocol population if they complete the study treatment period, have all assessments for the primary efficacy analysis and considered compliant. The patients are compliant if they do not have any major protocol violations in the course of the study.

8.3 SAFETY POPULATION

The Safety population is defined as all randomized subject who received at least one dose of study medication. The Safety population will therefore be identical to the ITT population if all randomized subject received at least one dose of study medication. The Safety population will be used to present all safety summaries, by actual treatment received.

9. STUDY PATIENTS

9.1 DISPOSITION

Patient distribution will be presented using descriptive statistic by treatment group. Following data will be presented: number of screened patients, number of patients in analysis populations, number of patients completed the study by the protocol and number of discontinued patients with discontinuation reasons.

9.2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic data and baseline characteristics will be presented using descriptive statistic for the ITT analysis populations.

Following parameters will be presented at screening:

- Age
- Gender
- Height
- Weight
- BMI
- Race
- Medical history
- Concomitant diseases
- Previous therapy
- Pregnancy test (for females)
- Oral cavity examination (only abnormal parameters)
- Vital signs (only abnormal parameters)

Between groups comparisons will be performed for:

- Age (ANOVA from LME model)
- Gender

[1] Baseline is Day 1 time 0 minutes

Number and percent of patients with previous medications will be presented as a frequency arrays by ATC (3 and 5 levels) and treatment groups.

Current and history diagnoses will be coded by MEDDRA dictionary. Data will be presented by SOC (System Organ Class) and PT (Preferred Term).

Frequencies of CS[1] oral cavity examination abnormalities at Day 1 will be summarized with descriptive statistics (absolute and relative frequencies). Table will show only CS abnormalities. No between group tests are planned.

Frequencies of CS vital signs abnormalities at Day 1 will be summarized with descriptive statistics (absolute and relative frequencies). Table will show only CS abnormalities. No between group tests are planned.

10. EFFICACY AND SAFETY ASSESMENT

Efficacy parameters will be assessed for the ITT population. Primary efficacy variable also be assessed for the PP population.

10.1 PRIMARY EFFICACY VARIABLE

Primary variable will be the $AUC_{0\text{-}}$6h without or with LOCF of pain intensity profile between time 0 (baseline value of VAS) and 6 hours post-treatment. $AUC_{0\text{-}6h}$ analysis will be based on **actual rather than scheduled timings** and will be calculated using the trapezoidal rule:

$$\sum \frac{P_n + P_{n-1}}{2}(t_n - t_{n-1})$$

where, P_n – pain intensity at point n, t_n – time point n.

Treatment AUCs will be compared using ANOVA methodology (simple GLM model). In case of significant covariates discovered during baseline data analysis, such covariates could be added to the ANOVA model (level to stay 0.15). F-test for type III treatment effect will be used for testing the Null hypothesis.

Null hypothesis (H_0) that OKITASK® is no different from Placebo will be rejected and alternative hypothesis (H_1) that OKITASK® is superior to Placebo will be accepted if mean $AUC_{0\text{-}6h}$ (OKITASK®) is less than mean $AUC_{0\text{-}6h}$ (Placebo) and $p < 0.05$.

$$\boldsymbol{H_0}: \boldsymbol{\mu_T} = \boldsymbol{\mu_R}$$

$$\boldsymbol{H_1}: \boldsymbol{\mu_T} \neq \boldsymbol{\mu_R}$$

where $\boldsymbol{\mu_T}$ – OKITASK® (**Test**) mean $AUC_{0\text{-}6h}$; $\boldsymbol{\mu_R}$ – Placebo (**Reference**) mean $AUC_{0\text{-}6h}$.

If the actual time is not recorded, the scheduled time will be used instead. LOCF approach will be applied as described in Section 7.

Additional test on FCS replaced data will be performed to confirm analysis of the LOCF data (sensitivity).

For the PP population data could not be missing. There were no LOCF or other methods applied.

10.2 SECONDARY EFFICACY

Secondary efficacy variables will be analyzed only for ITT population.

[1] Clinically significant

$AUC_{0\text{-}6h}$ without or with LOCF of pain relief profile between time 0 (baseline value of VAS) and 6 hours post-treatment. $AUC_{0\text{-}6h}$ analysis will be based on **actual rather than scheduled timings** and will be calculated using the trapezoidal rule (see as per primary variable).

Pain profile – Pain intensity profile will be analyzed using Analysis of Variance (ANOVA) for repeated measurements. The model will include fixed effect terms for clinical site, time point and treatment. Time point will be specified as a repeated measurement. In order to select an appropriate matrix for the observations within each subject, 3 models will be fitted using the compound symmetry, Huynh-Feldt and unstructured structures. The matrix for the final model will be selected using Akaike's Information Criterion where the lowest value indicates the best fit. The importance of the treatment-by-site interaction will be investigated but if the term is not significant at the 10% level, it will be excluded from the final model. The adjusted least squares mean will be estimated for each combination of time point and treatment. The estimated treatment difference between OKITASK® and placebo at each time point will be presented together with the corresponding 95% confidence interval. Pain profile will be analyzed based on **scheduled rather than actual timings.**

SAS code example:

```
proc mixed data=locf method=REML order=internal[1];
      class patid site trt time;
      model pain = trt time trt*time
                   site trt*site/ intercept ddfm=satterth;
      repeated time/ type=CS[2] subject=patid(trt);
      lsmeans trt*time/ diff=all cl;
run;
```

Pain relief – Pain relief will be analyzed in the same way.

LOCF replaced data of pain intensity and pain relief will be presented graphically by treatments and time points.

Time to first perceptible relief (TFPR)[3] – Kaplan-Meier curve and Log rank test will be used to describe and test treatment profile differences. In table it will be presented with median, 95% CI and p-value from Log rank test.

Time to meaningful pain relief (TMPR)[4] – Kaplan-Meier curve and Log rank test will be used to describe and test treatment profile differences. In table it will be presented with median, 95% CI and p-value from Log rank test.

Time to REMD – Time to rescue medication will be calculated for each subject and presented using only median value. If the number of subjects will be adequate Kaplan-Meier curve and Log rank test will be used to describe and test treatment profile differences.

Patient's overall assessment – will be described as nominal data (6 hours post-

[1] Data must be sorted!
[2] CS or HF or UN
[3] CRF data
[4] CRF data

dose). Mann-Whitney[1] test will be applied in order to test differences between treatments response.

10.3 SAFETY VARIABLES

- Concomitant medication
- Adverse events

10.3.1 Concomitant medication

Number and percent of patients with concomitant medications will be presented as a frequency arrays by ATC (3 and 5 levels) and treatment groups.

10.3.2 Adverse events and serious adverse events assessment

All adverse events will be coded with MedDRA dictionary (last available version at the moment of coding).

Before the start of statistical analysis all AEs will be qualified as TESS (AEs started after the first study drug dose or worsening conditions for previously available AEs) and not TESS. In case of missing dates in AE reporting dates will be replaced as described in section 7.

Adverse events of the study time (TESS) will be presented by frequencies (number of patients with AEs and number of events) grouped by treatment, System Organ Class (SOC) and Preferred terms (PT) and relation to the study drug and severity.

All AEs (TESS and not TESS) will be presented in listings.

Serious adverse events will be presented separated from all AEs with tables and listings.

11. AGREEMENTS

Statistical analysis will be performed using SAS 9.4 (www.sas.com).

11.1 DESCRIPTIVE STATISTICS

If there were no special cases all continuous data will be presented with a descriptive statistic by treatment group and other subgroups if necessary (time points/visits, for example). There will be presented a number of non-missing values, mean value with a standard deviation, median, minimum and maximum values, p-value of the normality test (Shapiro-Wilk). All values except p-value will be presented with one significant digit after comma, p-values will be presented with three significant digits or <0.001 (if any).

If there were no special cases all nominal and ordered data will be presented with absolute and relative frequencies (%) by treatment groups and subgroups (visits, for example).

11.2 OTHER

Calculation of time periods will be done relative to the date of the informed consent (IC).

[1] Proc Freq, CMH test, row-mean score difference

12. TABLE EXAMPLES[1]

Table 12.1 Disposition

	OKITASK® N = XX	PLACEBO N = XX
Screened		xx
Safety population	xx (xx.x%)	xx (xx.x%)
Intent-to-treat (ITT) population	xx (xx.x%)	xx (xx.x%)
Per-Protocol (PP) population	xx (xx.x%)	xx (xx.x%)
Study completion	xx (xx.x%)	xx (xx.x%)
Early termination	xx (xx.x%)	xx (xx.x%)
Adverse event	xx (xx.x%)	xx (xx.x%)
Death	xx (xx.x%)	xx (xx.x%)
Patient required rescue medication	xx (xx.x%)	xx (xx.x%)
Lost to follow-up	xx (xx.x%)	xx (xx.x%)
Consent withdrawn	xx (xx.x%)	xx (xx.x%)
Investigator decision	xx (xx.x%)	xx (xx.x%)
Protocol violation, including non-compliance	xx (xx.x%)	xx (xx.x%)
Patient required prohibited medications		
Protocol entry criteria not met	xx (xx.x%)	xx (xx.x%)
The patient starts of another study drug	xx (xx.x%)	xx (xx.x%)
Study is stopped by Sponsor decision	xx (xx.x%)	xx (xx.x%)
Study is stopped by regulatory instance / ethics committee	xx (xx.x%)	xx (xx.x%)
Pregnancy	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)

12.1 BASELINE AND DEMOGRAPHY

Table 12.2 Demographics. Screening (Day -4 to Day 1). ITT population. N = XX

Parameter	OKITASK® N = XX	PLACEBO N = XX
Age (years)		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min; Max	xx.x; xx.x	xx.x; xx.x
p-value ANOVA	0.xxx	
Gender		
Male	xx (xx.x%)	xx (xx.x%)
Female	xx (xx.x%)	xx (xx.x%)
No data[2]	xx (xx.x%)	xx (xx.x%)
p-value χ^2or Fisher	0.xxx	
Race		
No data[3]	xx (xx.x%)	xx (xx.x%)
Caucasian	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)
Height (cm)		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min; Max	xx.x – xx.x	xx.x – xx.x
Weight (kg)		
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min; Max	xx.x – xx.x	xx.x – xx.x
BMI (kg/m^2)		

[1] Tables in the statistical report could be differ from these examples but all necessary information will be presented
[2] if any
[3] if any

Parameter	OKITASK® N = XX	PLACEBO N = XX
N	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Min; Max	xx.x – xx.x	xx.x – xx.x

Table 12.3 Medical history. Screening (Day -4 to Day 1). ITT population. N = XX

System Organ Class term Preferred term	OKITASK® N = XX	PLACEBO N = XX
Total patients	xx (xx.x%)	xx (xx.x%)
SOC term	xx (xx.x%)	xx (xx.x%)
Preferred term 1	xx (xx.x%)	xx (xx.x%)
Preferred term 2	xx (xx.x%)	xx (xx.x%)
…		

Table 12.4 Concomitant[1] diseases. Screening (Day -4 to Day 1). ITT population. N = XX

Similar

Table 12.5 Previous therapy. Screening (Day -4 to Day 1). ITT population. N = XX

ATC Group Drug (ATC code)	OKITASK® N = XX	PLACEBO N = XX
ATC Group (level 3)	**xx (xx.x%)**	**xx (xx.x%)**
Drug 1 (ATC level 5)	xx (xx.x%)	xx (xx.x%)
Drug 2 (ATC level 5)	xx (xx.x%)	xx (xx.x%)
…		

Table 12.6 Pregnancy test. Screening (Day -4 to Day 1). Females. ITT population. N = XX

	OKITASK® N = XX	PLACEBO N = XX
Positive	xx (xx.x%)	xx (xx.x%)
Negative	xx (xx.x%)	xx (xx.x%)
Not applicable	xx (xx.x%)	xx (xx.x%)
No data[2]	xx (xx.x%)	xx (xx.x%)

Table 12.7 Oral cavity examination. Screening (Day -4 to Day 1). ITT population. N = XX

CS[3] Abnormalities only[4]	OKITASK® N = XX	PLACEBO N = XX
General appearance	xx (xx.x%)	xx (xx.x%)
Condition of mucous membranes	xx (xx.x%)	xx (xx.x%)
Teeth	xx (xx.x%)	xx (xx.x%)
Throat	xx (xx.x%)	xx (xx.x%)

[1] Flag “ongoing” is set
[2] if any
[3] Clinically significant
[4] Parameters with normal values or NCS (not clinically significant) in both groups should be omitted from this table

Table 12.8 Vital signs. Screening (Day -4 to Day 1). ITT population. N = XX

CS[1] Abnormalities only[2]	OKITASK® N = XX	PLACEBO N = XX
Pulse rate (beats/min)	xx (xx.x%)	xx (xx.x%)
Respiratory rate (/min)	xx (xx.x%)	xx (xx.x%)
Systolic blood pressure (mm Hg)	xx (xx.x%)	xx (xx.x%)
Diastolic blood pressure (mm Hg)	xx (xx.x%)	xx (xx.x%)
Body temperature (oral cavity) (°C)	xx (xx.x%)	xx (xx.x%)

12.2 EFFICACY

12.2.1 Primary efficacy

Table 12.9 Primary efficacy. Visual Analogue Scale. Pain Intensity Assessment with LOCF. ITT population. N = XX

Parameter / Treatment	Result				
	N	Mean (SD)	Median	Min	Max
Visual Analogue Scale. Pain Intensity. AUC_{0-6h}. LOCF					
OKITASK ®	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
PLACEBO	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
p-value ANOVA = 0.xxx					
Visual Analogue Scale. Pain Intensity. AUC_{0-6h}. Multiple Imputation					
OKITASK ®	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
PLACEBO	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
p-value ANOVA = 0.xxx					

Table 12.10 Primary efficacy. Visual Analogue Scale. Pain Intensity Assessment without LOCF. PP population. N = XX

Parameter / Treatment	Result				
	N	Mean (SD)	Median	Min	Max
Visual Analogue Scale. Pain Intensity. AUC_{0-6h}					
OKITASK ®	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
PLACEBO	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
p-value ANOVA = 0.xxx					

Table 12.11 Primary efficacy. Visual Analogue Scale. Pain Intensity Assessment with LOCF. ITT population. N = XX

Parameter / Treatment	Result				
	N	Mean (SD)	Median	Min	Max
Visual Analogue Scale. Pain Intensity. AUC_{0-6h}. LOCF					
OKITASK ®	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
PLACEBO	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
p-value ANOVA = 0.xxx					
Visual Analogue Scale. Pain Intensity. AUC_{0-6h}. Multiple Imputation					
OKITASK ®	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
PLACEBO	xx	xx.x (xx.x)	xx.x	xx.x	xx.x

[1] Clinically significant
[2] Parameters with normal values or NCS (not clinically significant) in both groups should be omitted from this table

Parameter Treatment	Result N	Mean (SD)	Median	Min	Max
p-value ANOVA = 0.xxx					

Table 12.12 Primary efficacy. Visual Analogue Scale. Pain Intensity Assessment without LOCF. PP population. N = XX

Parameter Treatment	Result N	Mean (SD)	Median	Min	Max
Visual Analogue Scale. Pain Intensity. AUC_{0-6h}					
OKITASK ®	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
PLACEBO	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
p-value ANOVA = 0.xxx					

12.2.2 Secondary efficacy

Table 12.13 secondary efficacy. Visual Analogue Scale. Pain Intensity Assessment with LOCF. ITT population. N = XX

Parameter Treatment	Result N	Mean (SD)	Median	Min	Max
Visual Analogue Scale. Pain Intensity. AUC_{0-6h}. LOCF					
OKITASK ®	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
PLACEBO	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
p-value ANOVA = 0.xxx					
Visual Analogue Scale. Pain Intensity. AUC_{0-6h}. Multiple Imputation					
OKITASK ®	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
PLACEBO	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
p-value ANOVA = 0.xxx					

Table 12.14 secondary efficacy. Visual Analogue Scale. Pain Intensity Assessment with LOCF. ITT population. N = XX

Parameter Treatment	Result N	Mean (SD)	Median	Min	Max
Visual Analogue Scale. Pain Intensity. AUC_{0-6h}. LOCF					
OKITASK ®	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
PLACEBO	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
p-value ANOVA = 0.xxx					
Visual Analogue Scale. Pain Intensity. AUC_{0-6h}. Multiple Imputation					
OKITASK ®	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
PLACEBO	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
p-value ANOVA = 0.xxx					

Table 12.15 Secondary efficacy. Visual Analogue Scale. Pain Intensity profile. ITT population. N = XX

Parameter Treatment	Day 1 time	Results N	Mean (SD)	Median	Min	Max

Parameter Treatment	Day 1 time	Results				
		N	Mean (SD)	Median	Min	Max
Visual Analog Scale. Pain intensity						
OKITASK ®	0 min. Baseline	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
PLACEBO	0 min. Baseline	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
$\mu_T - \mu_R$ 95% CI			xx.x [xx.x; xx.x]			
OKITASK ®	5 minutes	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
PLACEBO	5 minutes	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
$\mu_T - \mu_R$ 95% CI			xx.x [xx.x; xx.x]			
…						
OKITASK ®	6 hours	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
PLACEBO	6 hours	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
$\mu_T - \mu_R$ 95% CI			xx.x [xx.x; xx.x]			

Figure 12.1 Secondary efficacy. Visual Analogue Scale. Pain Intensity profile. ITT population. N = XX

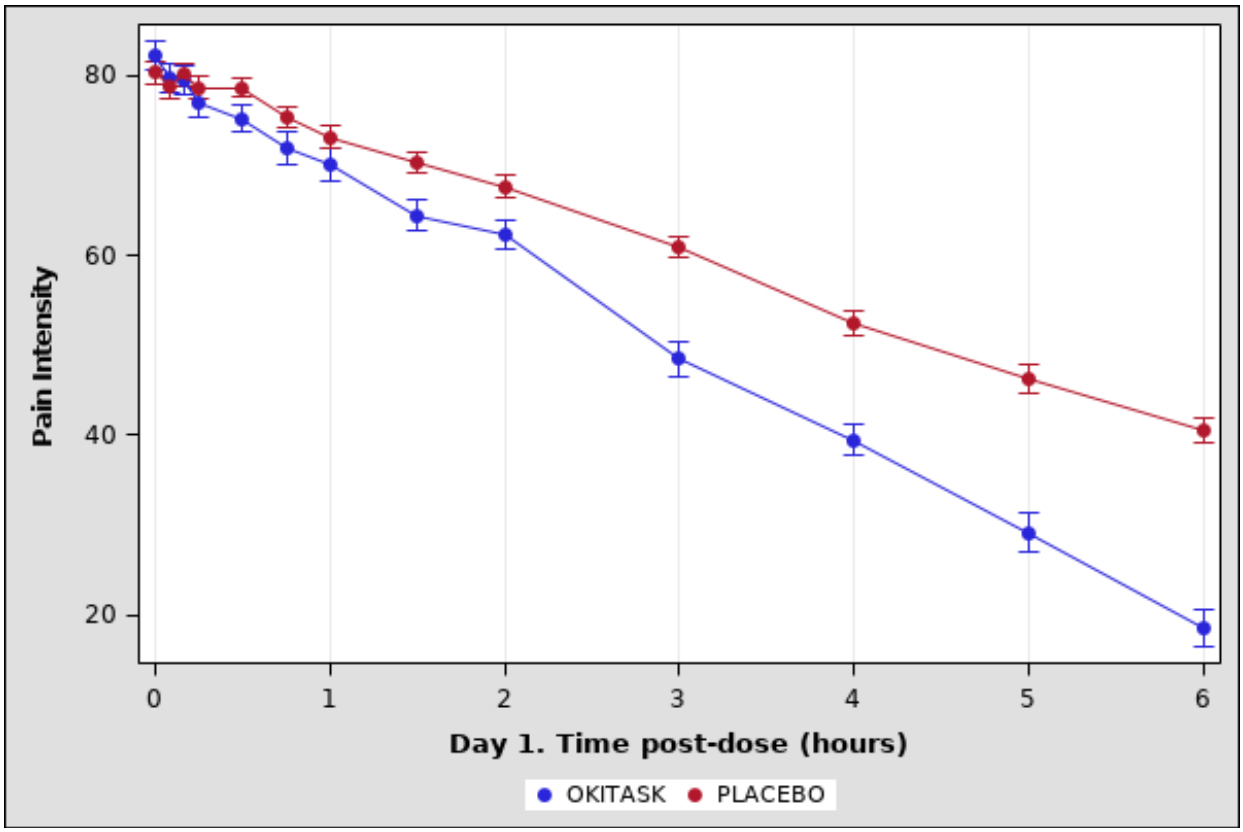

Figure 12.2 Secondary efficacy. Visual Analogue Scale. Difference in Pain Intensity means with 95% CI. ITT population. N = XX

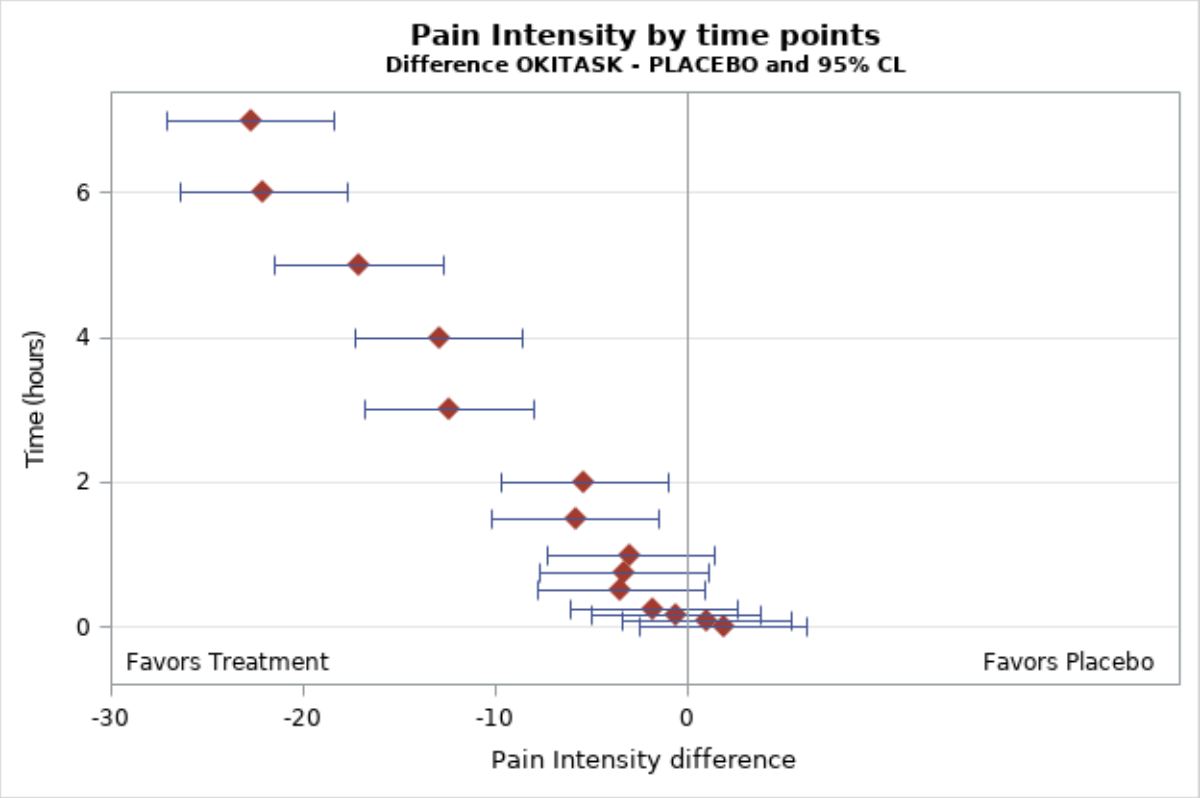

Table 12.16 Secondary efficacy. Visual Analogue Scale. Pain Relief profile. ITT population. N = XX

Parameter / Treatment	Day 1 time	Results				
		N	Mean (SD)	Median	Min	Max
Visual Analog Scale. Pain relief						
OKITASK ®	0 min. Baseline	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
PLACEBO	0 min. Baseline	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
$\mu_T - \mu_R$ 95% CI			xx.x [xx.x; xx.x]			
OKITASK ®	5 minutes	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
PLACEBO	5 minutes	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
$\mu_T - \mu_R$ 95% CI			xx.x [xx.x; xx.x]			
…						
OKITASK ®	6 hours	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
PLACEBO	6 hours	xx	xx.x (xx.x)	xx.x	xx.x	xx.x
$\mu_T - \mu_R$ 95% CI			xx.x [xx.x; xx.x]			

Figure 12.3 Secondary efficacy. Visual Analogue Scale. Pain Relief profile. ITT population. N = XX

Similar to Figure 12.1

Figure 12.4 Secondary efficacy. Visual Analogue Scale. Difference in Pain Relief means with 95% CI. ITT population. N = XX

Similar to Figure 12.2

Table 12.17 Time to first perceptible relief (TFPR) and Time to meaningful pain relief (TMPR). ITT population. N = XX

Parameter Treatment	Median 95% CI
Time to first perceptible relief (TFPR) hours	
OKITASK®	xx.x [xx.x; xx.x]
PLACEBO	xx.x [xx.x; xx.x]
Log rank test p-value	0.xxx
Time to meaningful pain relief (TMPR) hours	
OKITASK®	xx.x [xx.x; xx.x]
PLACEBO	xx.x [xx.x; xx.x]
Log rank test p-value	0.xxx

Table 12.18 Time to rescue medication (REMD). ITT population. N = XX

Parameter Treatment	Median	Median 95% CI[1]
Time to rescue medication (REMD) hours		
OKITASK®	xx.x	xx.x [xx.x; xx.x]
PLACEBO	xx.x	xx.x [xx.x; xx.x]
Log rank test p-value		0.xxx

Table 12.19 Overall assessment 6-hours post-dose. ITT population. N = XX

	OKITASK® N = XX	PLACEBO N = XX
(1) Very good	xx (xx.x%)	xx (xx.x%)
(2) Good	xx (xx.x%)	xx (xx.x%)
(3) Satisfactory	xx (xx.x%)	xx (xx.x%)
(4) Poor	xx (xx.x%)	xx (xx.x%)
(5) Very poor	xx (xx.x%)	xx (xx.x%)
No data[2]	xx (xx.x%)	xx (xx.x%)
p-CMH		0.xxx

12.3 SAFETY PARAMETERS

Table 12.20 Concomitant medication. During the study time. Safety population. N = XX

ATC Group Drug (ATC code)	OKITASK® N = XX	PLACEBO N = XX
ATC Group (level 3)	**xx (xx.x%)**	**xx (xx.x%)**
Drug 1 (ATC level 5)	xx (xx.x%)	xx (xx.x%)
Drug 2 (ATC level 5)	xx (xx.x%)	xx (xx.x%)
…		

Table 12.21 Adverse events. Summary table. Safety population. N = XX

Parameter	OKITASK® N = XX		PLACEBO N = XX	
	x (%)	*Y*	*x (%)*	*Y*
Patients with AE/SAE	xx (xx.x%)	xx	xx (xx.x%)	xx
Patients with SAE	xx (xx.x%)	xx	xx (xx.x%)	xx
Patients with death outcome AE/SAE	xx (xx.x%)	xx	xx (xx.x%)	xx
Patients with mild and moderate AE/SAE	xx (xx.x%)	xx	xx (xx.x%)	xx
Patients with severe AE/SAE	xx (xx.x%)	xx	xx (xx.x%)	xx
Patients with related or possibly related AE/SAE	xx (xx.x%)	xx	xx (xx.x%)	xx
Patients with related or possibly related severe AE/SAE	xx (xx.x%)	xx	xx (xx.x%)	xx

[1] If data allow
[2] if any

Parameter	OKITASK® N = XX		PLACEBO N = XX	
	x (%)	*Y*	*x (%)*	*Y*
Patients with AE/SAE leaded to discontinuation	xx (xx.x%)	xx	xx (xx.x%)	xx

X = patients with at least one event in the group
% = percent of patients with at least one event in the group
Y = total number of events

Table 12.22 Adverse events started before taking the first drug dose. Safety population. N = XX

MEDDRA System Organ Class term *MEDDRA Preferred term*	OKITASK®		PLACEBO	
	x (%)	*Y*	*x (%)*	*Y*
Patients with AEs/SAEs	xx (xx.x%)		xx (xx.x%)	
SOC term	xx (xx.x%)	xx	xx (xx.x%)	xx
Preferred term 1	xx (xx.x%)	xx	xx (xx.x%)	xx
Preferred term 2	xx (xx.x%)	xx	xx (xx.x%)	xx
…				

X = patients with at least one event in the group
% = percent of patients with at least one event in the group
Y = total number of events

Table 12.23 Adverse events. Safety population. N = XX

MEDDRA System Organ Class term *MEDDRA Preferred term*	OKITASK®		PLACEBO	
	x (%)	*Y*	*x (%)*	*Y*
Patients with AEs/SAEs	xx (xx.x%)		xx (xx.x%)	
SOC term	xx (xx.x%)	xx	xx (xx.x%)	xx
Preferred term 1	xx (xx.x%)	xx	xx (xx.x%)	xx
Preferred term 2	xx (xx.x%)	xx	xx (xx.x%)	xx
…				

X = patients with at least one event in the group
% = percent of patients with at least one event in the group
Y = total number of events

Table 12.24 Adverse events and relation to the study drug. Safety population. N = XX

MEDDRA System Organ Class term *MEDDRA Preferred term*	Relation	OKITASK®		PLACEBO	
		x (%)	*Y*	*x (%)*	*Y*
Patients with AE/SAE		xx (xx.x%)		xx (xx.x%)	
	Highly probable	xx (xx.x%)		xx (xx.x%)	
	Probable	xx (xx.x%)		xx (xx.x%)	
	Possibly	xx (xx.x%)		xx (xx.x%)	
	Unlikely	xx (xx.x%)		xx (xx.x%)	
	None	xx (xx.x%)		xx (xx.x%)	
SOC term		xx (xx.x%)	xx	xx (xx.x%)	xx
Preferred term 1	**Probable**	xx (xx.x%)	xx	xx (xx.x%)	xx
	Possibly	xx (xx.x%)	xx	xx (xx.x%)	xx
	Unlikely	xx (xx.x%)	xx	xx (xx.x%)	xx
	None	xx (xx.x%)	xx	xx (xx.x%)	xx
Preferred term 2		xx (xx.x%)	xx	xx (xx.x%)	xx
…					

X = patients with at least one event in the group
% = percent of patients with at least one event in the group
Y = total number of events

Table 12.25 Adverse events and relation to the study drug (related/not related). Safety population. N = XX

MEDDRA System Organ Class term *MEDDRA Preferred term*	Relation	OKITASK® *x (%)*	*Y*	PLACEBO *x (%)*	*Y*
Patients with AE/SAE		xx (xx.x%)		xx (xx.x%)	
	Related[1]	xx (xx.x%)		xx (xx.x%)	
	Not related[2]	xx (xx.x%)		xx (xx.x%)	
SOC term		xx (xx.x%)	xx	xx (xx.x%)	xx
Preferred term 1	**Related**	xx (xx.x%)	xx	xx (xx.x%)	xx
	Not related	xx (xx.x%)	xx	xx (xx.x%)	xx
Preferred term 2		xx (xx.x%)	xx	xx (xx.x%)	xx
…					

X = patients with at least one event in the group
% = percent of patients with at least one event in the group
Y = total number of events

Table 12.26 Adverse events with severity. Safety population. N = XX

MEDDRA System Organ Class term *MEDDRA Preferred term*	Severity	OKITASK® *x (%)*	*Y*	PLACEBO *x (%)*	*Y*
Patients with AE/SAE		xx (xx.x%)		xx (xx.x%)	
	Mild	xx (xx.x%)		xx (xx.x%)	
	Moderate	xx (xx.x%)		xx (xx.x%)	
	Severe	xx (xx.x%)		xx (xx.x%)	
SOC term		xx (xx.x%)	xx	xx (xx.x%)	xx
Preferred term 1	**Mild**	xx (xx.x%)	xx	xx (xx.x%)	xx
	Moderate	xx (xx.x%)	xx	xx (xx.x%)	xx
	Severe	xx (xx.x%)	xx	xx (xx.x%)	xx
Preferred term 2		xx (xx.x%)	xx	xx (xx.x%)	xx
…					

X = patients with at least one event in the group
% = percent of patients with at least one event in the group
Y = total number of events

Table 12.27 Serious adverse events. Safety population. N = XX

MEDDRA System Organ Class term *MEDDRA Preferred term*	OKITASK® *x (%)*	*Y*	PLACEBO *x (%)*	*Y*
Patients with SAEs	xx (xx.x%)		xx (xx.x%)	
SOC term	xx (xx.x%)	xx	xx (xx.x%)	xx
Preferred term 1	xx (xx.x%)	xx	xx (xx.x%)	xx
Preferred term 2	xx (xx.x%)	xx	xx (xx.x%)	xx
…				

X = patients with at least one event in the group
% = percent of patients with at least one event in the group
Y = total number of events

[1] Highly or Probable or Possible related
[2] Unlikely related or None

Table 12.28 Serious adverse events and relation to the study drug. Safety population. N = XX

MEDDRA System Organ Class term *MEDDRA Preferred term*	Relation	OKITASK®		PLACEBO	
		x (%)	*Y*	*x (%)*	*Y*
Patients with SAE		xx (xx.x%)		xx (xx.x%)	
	Highly probable	xx (xx.x%)		xx (xx.x%)	
	Probable				
	Possibly	xx (xx.x%)		xx (xx.x%)	
	Unlikely	xx (xx.x%)		xx (xx.x%)	
	None	xx (xx.x%)		xx (xx.x%)	
SOC term		xx (xx.x%)	xx	xx (xx.x%)	xx
Preferred term 1	**Probable**	xx (xx.x%)	xx	xx (xx.x%)	xx
	Possibly	xx (xx.x%)	xx	xx (xx.x%)	xx
	Unlikely	xx (xx.x%)	xx	xx (xx.x%)	xx
	None	xx (xx.x%)	xx	xx (xx.x%)	xx
Preferred term 2		xx (xx.x%)	xx	xx (xx.x%)	xx
…					

X = patients with at least one event in the group
% = percent of patients with at least one event in the group
Y = total number of events

Table 12.29 Serious adverse events and relation to the study drug (related/not related). Safety population. N = XX

MEDDRA System Organ Class term *MEDDRA Preferred term*	Relation	OKITASK®		PLACEBO	
		x (%)	*Y*	*x (%)*	*Y*
Patients with SAE		xx (xx.x%)		xx (xx.x%)	
	Related[1]	xx (xx.x%)		xx (xx.x%)	
	Not related[2]	xx (xx.x%)		xx (xx.x%)	
SOC term		xx (xx.x%)	xx	xx (xx.x%)	xx
Preferred term 1	**Related**	xx (xx.x%)	xx	xx (xx.x%)	xx
	Not related	xx (xx.x%)	xx	xx (xx.x%)	xx
Preferred term 2		xx (xx.x%)	xx	xx (xx.x%)	xx
…					

X = patients with at least one event in the group
% = percent of patients with at least one event in the group
Y = total number of events

Table 12.30 Serious adverse events with severity. Safety population. N = XX

MEDDRA System Organ Class term *MEDDRA Preferred term*	Severity	OKITASK®		PLACEBO	
		x (%)	*Y*	*x (%)*	*Y*
Patients with SAE		xx (xx.x%)		xx (xx.x%)	
	Mild	xx (xx.x%)		xx (xx.x%)	
	Moderate	xx (xx.x%)		xx (xx.x%)	
	Severe	xx (xx.x%)		xx (xx.x%)	
SOC term		xx (xx.x%)	xx	xx (xx.x%)	xx
Preferred term 1	**Mild**	xx (xx.x%)	xx	xx (xx.x%)	xx
	Moderate	xx (xx.x%)	xx	xx (xx.x%)	xx
	Severe	xx (xx.x%)	xx	xx (xx.x%)	xx
Preferred term 2		xx (xx.x%)	xx	xx (xx.x%)	xx
…					

X = patients with at least one event in the group
% = percent of patients with at least one event in the group
Y = total number of events

[1] Highly or Probable or Possible related
[2] Unlikely related or None

12.4 LISTINGS

Listing 12.1 Adverse events. Listing

Site-patient number	Gender	Age 9years)	Treatment	AE number	AE description	MEDDRA System Organ Class	Preferred Term	Low Level Term	AE start date	AE start day of treatment	AE stop date	AE stop day of treatment	Relation to the study drug	Severity	Actions taken	Therapy due to AE	Outcome	Serious?
xx-xxxx	XXXXXX	xx.x	XXXXXXX	1	xxxxxxxxxxx	xxxxxxxxxxx	xxxxxxxxxxx	xxxxxxxxxxx	xxxx-xx-xx	xxx	xxxx-xx-xx	xxxx	xxxx	xxxx	xxxx	xxx	xxxxxx	xxxx
xx-xxxx	XXXXXX	xx.x	XXXXXXX	1	xxxxxxxxxxx	xxxxxxxxxxx	xxxxxxxxxxx	xxxxxxxxxxx	xxxx-xx-xx	xxxx	xxxx-xx-xx	xxx	xxxx	xxxx	xxxx	xxx	xxxxxx	xxxx