CONFIDENTIAL

Statistical Analysis Plan (SAP)

Sponsor:	**Integrative Research Laboratories AB**
Study code:	**IRL790C003**
Study title:	**A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE IIA STUDY EVALUATING THE EFFICACY AND TOLERABILITY OF IRL790 IN PARKINSON'S DISEASE DYSKINESIA**
Date:	**04JUL2018 – Draft 1** **15MAY2019 – Draft 2** **20MAY2019 – Final** **13JUN2019 – Final V02**

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1 LIST OF ABBREVIATIONS

AE – Adverse Event

ATC – Anatomical-Therapeutic-Chemical

CF – Clean File

CRF – Case Report Form

CSP – Clinical study protocol

FAS – Full Analysis Set

MedDRA – Medical Dictionary for Regulatory Affairs

PPS – Per Protocol Set

SAE – Serious Adverse Event

SAP – Statistical Analysis Plan

SAS – Statistical Analysis System

SD – Standard Deviation

2 INTRODUCTION

This Statistical Analysis Plan (SAP) gives details regarding the statistical analyses and data presentation outlined in the final Clinical study protocol (CSP) for the study *IRL790C003_Protocol_V36_14Nov1714Jan2019.* Any changes from the final CSP are given in Section 8.

3 CLINICAL STUDY DETAILS

3.1 Clinical Study Objectives

3.1.1 Primary objective

The primary objective of the study is to evaluate the effects of IRL790 on levodopa induced dyskinesia in patients with Parkinson's disease.

3.1.2 Primary endpoint

Change in the Unified Dyskinesia Rating Scale (UDysRS) total score from Baseline (Day 1) to Visit 4 (Day 28 End of Treatment or earlier in the event of withdrawal).

3.1.3 Secondary objectives

The secondary objectives of the study are:

1. To evaluate the effects of adjunctive treatment with IRL790 on levodopa induced dyskinesia assessed with the total objective score (part III + IV) in the Unified Dyskinesia Rating Scale (UDysRS), as compared to placebo.
2. To evaluate the effects of adjunctive treatment with IRL790 on symptoms of PD assessed with Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part II + III (motor aspects of experiences of daily living (M-EDL + motor examination (ME)), and sum of Questions 4.1 and 4.2 (dyskinesia) in part IV (motor complications) as compared to placebo.
3. To evaluate the effects of adjunctive treatment with IRL790 on the daily motor "OFF" time as assessed by patient completed 24-hour diaries, as compared to placebo

3.1.4 Secondary endpoints

- Change in Total Objective Score (III, IV) of the UDysRS from Baseline (Day 1) to Visit 4 (Day 28).
- Change in total daily "OFF" time as assessed by patient completed 24-hour diaries, from run-in to Visit 4 (Day 28).
- Change in Unified Parkinson's Disease Rating Scale (MDS-UPDRS) sum score of part II+ III (M-EDL+ ME)).
- Change in sum score of Questions 4.1 and 4.2 (dyskinesia) in MDS-UPDRS part IV to Visit 4 (Day 28).

3.1.5 Exploratory endpoints

Additionally, a number of exploratory end points will be assessed. The following items will be assessed:

- Unified Parkinson's Disease Rating Scale (MDS-UPDRS), part I (total score), part II (total score), part III (total score) and part IV (total score) from Baseline (Day 1) to Visit 4 (Day 28).
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Question 1.2 (Hallucinations and Psychosis) from Baseline (Day 1) to Visit 4 (Day 28).
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Question 1.6 (Features of dopamine dysregulation syndrome) from Baseline (Day 1) to Visit 4 (Day 28).
- Change in sum score of Questions 4.3, 4.4 and 4.5 (motor fluctuations) in MDS-UPDRS part IV to Visit 4 (Day 28).
- Change in sum score of Questions 3.15 and 3.16 (postural and kinetic tremor of the hands) in MDS-UPDRS part III to Visit 4 (Day 28).
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Question 4.3 (Time spent in the off state) from Baseline (Day 1) to Visit 4 (Day 28).
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Question 4.6 (Painful off state dystonia) from Baseline (Day 1) to Visit 4 (Day 28).
- UDysRS part 1 (Historical on-dyskinesia)
- UDysRS part 2 (Historical off-dystonia)
- UDysRS part 1+2 (Historical dyskinesia)
- Change in ”ON” time with troublesome dyskinesia as assessed by patient completed 24-hour diaries, from run-in to Visit 4 (Day 28).
- Change in ”ON” time as assessed by patient completed 24-hour diaries, from run-in to Visit 4 (Day 28).
- Change in Sleep time as assessed by patient completed 24-hour diaries, from run-in to Visit 4 (Day 28).

3.2 Clinical Study Design

This is a multi-centre, randomised, double-blind, placebo-controlled trial with the primary objective to evaluate the efficacy of 28 days’ treatment with IRL790 in patients with PD experiencing LID.

Consenting patients will be screened for eligibility according to study-specific inclusion/exclusion criteria (see protocol sections 4.2 and 4.3) within 7-28 days before start of IMP administration (Screening Visit).

At the Screening visit patients will be instructed and trained to complete two 24-hour diaries for assessment of daily motor function and to bring the completed diaries to the clinic at Visit 1. Patients completing at least one valid diary will be eligible for inclusion.

Following baseline assessments at Visit 1 (Day 1) patients will be randomised to receive IRL790 or placebo (1:1 randomisation). The treatment allocation will be double-blinded, i.e. it will not

be disclosed to the patients, the site staff or the Sponsor (see protocol Section 6.4). Study medication will be dispensed and the first capsules of IMP will be administered in the clinic. The patient will be instructed to take the second daily dose in the afternoon of the same day as the study visit.

During the treatment period, Visits 2-4 will be performed on Days 7, 14 and 28 and a follow-up phone call on Day 21. Dose adjustments of IRL790 will be made as described in protocol Section **Error! Reference source not found.**.

During the telephone follow-up call on Day 21, the patient will be asked to complete two 24-hour diaries for assessment of daily motor function and bring the completed diaries to the clinic at Visit 4 on Day 28.

On Day 28 (Visit 4) the morning IMP dose will be administered at the clinic. ECG will be assessed two hours after IMP administration. Blood samples for PK analysis will be collected pre-dose and two hours post dose.

The MDS-UPDRS part 3 will be assessed with the patient in the “on state” on Day 1 (Visit 1) and Day 28 (Visit 4 End of Treatment or earlier in the event of withdrawal).

To assess dyskinesia, the UDysRS will be administered on Day 1 (Visit 1) and Day 28 (Visit 4 End of Treatment or earlier in the event of withdrawal). The physician rated part III will be assessed with the patients in the “on” state. Patients will be filmed using the “Rush filming protocol” (see protocol Appendix **Error! Reference source not found.**) in the “on” state. The film sequences will be transferred to a blinded Central Rater for assessment and the results from this rating will subsequently be included in the CRF.

A follow-up visit will take place 5-8 days after the last IMP dose.

Unscheduled visits will be performed as needed during the study and should be documented in the appropriate section of the CRF.

3.3 Number of Subjects

A total number of 74 patients will be required.

3.4 Methods of Assigning Subject to IMP

This is a double-blind study, thus, the study patients and the site personnel who are making the study assessments will be blinded to the study treatments of IRL790 and Placebo (capsules of IRL790 and placebo will be of identical appearance.).

Treatment allocation (1:1 randomisation) will be performed via a web-based IVRS and based on the randomisation list generated by Endpoint Clinical

4 STATISTICAL AND ANALYTICAL PLANS

4.1 Sample Size Justification

Seventy-Four (74) patients (37 per group) are sufficient to demonstrate an effect size of 0.67 between the active treatment and control (IRL790 vs Placebo) for the UDysRS primary endpoint with 80% power and type 1 error rate 0.05 (two tailed).

The effect size used is derived from the mean difference between the active and control groups (at the end of the treatment period) standardised according to the pooled 'between' group standard deviation. Estimates for these were obtained from published literature (Table 1).

Table 1: Sources For Effect Size

Reference	Mean Difference (A-P) (Diff) (n per group) After X Weeks Treatment	Pooled Standard Deviation	Effect Size[1]
Goetz (2013)	31-23 (14) (30 per group) 4wks Actual values	~12	0.58
Pahwa (2017)	16 - 8 (8) (60 per group) 12wks Change from baseline	~12.3 (SE:1.6)	0.65[2]
Pahwa (2015)	16.7 - 6.7 (10) (20 per group) 8wks Change from baseline	~13 (SE: 3)	0.77[3]

4.2 Definition of Analysis Sets

4.2.1 Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomised and treated patients who receive one or more doses and who provide post baseline data whether or not they fully comply with the requirements of the protocol. However, given the stage of development patients will be analysed according to the treatment they actually receive in the event of randomisation errors and not according to the scheduled treatment assignment.

4.2.2 Per Protocol Analysis Set

The Per Protocol Set (PPS) will consist of patients from the FAS but exclude those with major protocol violations. All protocol deviations will be reviewed prior to database lock and situations which constitute major protocol violations and constitute reasons for exclusion from the PPS will be defined and documented in the clean file report.

4.2.3 Safety Analysis Set

The Safety Set (SS) will consist of all patients who receive at least one dose of study drug. All safety and tolerability evaluations will be based on this analysis set. Again, patients who receive the wrong treatment according to the randomisation schedule will be analysed according to the treatment actually received.

The SS population will be applied to all safety and tolerability assessments and analyses.

4.2.4 Use of analysis set

Patients who are to be included in and excluded from the PPS will be identified and listed following a Blind Data Review performed prior to the conclusion of the clinical investigation, database lock and unblinding.

Statistical analyses for the primary and secondary endpoints will be performed using both the FAS and PPS. Although the FAS is considered of primary importance, the PPS will enable evaluation of the sensitivity and robustness of the estimates of the magnitude of the treatment effect

All other evaluations will involve the FAS population (i.e.: Demographic and baseline characteristics, Exploratory investigations, Pharmacokinetics).

[1] NB: Smaller effect size = larger sample size required to detect difference
[2] n per group approx 37 with 80% power
[3] n per group approx 28 with 80% power

4.3 Definition of Baseline

Baseline measurement is defined as the latest measurement prior to first dose of IMP.

4.4 Summary Statistics

In general, all data collected will be presented with summary statistics and given in patient data listings. Summary statistics will include at least number of patients, mean, standard deviation, median, minimum and maximum for continuous data and frequency and percentage for categorical data. Tables with summary statistics will be divided by treatment group and dose group and visit where applicable. Patient data listings will be sorted by treatment, subject and timing of assessments.

4.5 Significance Level

A significance level of 5% will be applied.

4.6 Multiple Comparisons/Multiplicity

No adjustments for multiplicity will be performed. All statistically significant results must be judged by study physician in order to declare clinical relevance.

4.7 Handling of Drop-outs, Missing Data and Outliers

Outliers will be included in summary tables and listings and will not be handled separately in any analyses.

In the event of missing data for the any of the endpoints at baseline will as the primary analysis the baseline value be set to missing, and as a sensitivity analysis will the mean value of all patients be imputed as baseline value.

In the event of missing data at Visit 4 (last efficacy visit) for any of the endpoints will as the primary analysis the Visit 4 value be kept as missing and as a sensitivity analysis will the baseline value be imputed as Visit 4 value.

No imputation of individual questions will be performed.

4.8 Adjustment for Covariates

Only baseline measurement will be used as covariate for the absolute change analysis.

4.9 Multicenter Studies

No adjustment or analyses for site will be applied.

4.10 Examination of Subgroups

Subjects randomized to IRL790 treatment will be analysed by final dosing (and compared to placebo as one group and within IRL790) according to the following:

1. Subjects prescribed 5mg b.i.d (or a lower dose)
2. Subjects prescribed 7.5mg b.i.d. or a higher dose

4.11 Blind Review

Not applicable.

5 SUBJECTS

5.1 Subject Disposition

The number of subjects that entered the study, withdrawn subjects, completed subjects and the number of subjects at each visit will be summarized by treatment.

5.2 Baseline Characteristics and Demographics

This will include all assessments performed prior to the start of treatment (Screening) including Demographics (Gender, Age, Ethnic Origin), Medical history, Diagnosis of PD, Duration of PD, Height, Weight, BMI, MMSE, Hoehn and Yahn Scale score and Prior medications. Each will be described overall and according to treatment group.

6 TREATMENT INFORMATION AND EXTENT OF EXPOSURE

6.1 Compliance

At the conclusion of treatment period an assessment of compliance with the required dosing schedule will be performed and summarised by treatment group (((total tablets taken - total prescribed)/total prescribed)*100%).

6.2 Prior and Concomitant Medications

Concomitant medication will be summarised by Anatomical Therapeutic Chemical (ATC) code levels 2 and 4 using the World Health Organisation Drug dictionary (WHODD) with the number and percentage of patients by treatment group and overall

7 STATISTICAL METHODOLOGY

All parameters will be presented by treatment and visit using summary statistics. Additional statistical analyses are specified below.

7.1 Primary endpoint

7.1.1 Definition

The primary efficacy variable is the UDysRS total score. The change from baseline will be defined as absolute change.

This rating scale has two primary sections: Historical [Part 1 (On-Dyskinesia) and Part 2 (Off-Dystonia)], Objective [Part 3 (Impairment) and Part 4 (Disability)]. The Historical part has 15 items and the Objective part 11 items with each item having 0-4 ratings, where 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe. The subtotals for both the Historical and Objective parts are summed to give an overall score.

7.1.2 Analyses

The Primary endpoint can be considered quantitative continuous data (Interval in type). As such the Change from baseline to End of Treatment (Visit 4, Day 28 or earlier in the event of withdrawal) will be derived for each patient and analysed using an Analysis of Covariance (ANCOVA) model to compare the two treatment groups (IRL790 vs Placebo).

The ANCOVA analysis will allow estimation of the size of treatment effects as well as magnitude of differences between the active treatment and control (IRL790 - Placebo). The dependent variable will be the Change from baseline value and Treatment group the explanatory (independent) variable and fixed factor. A baseline covariate term will be included to ensure minimum variance unbiased estimation

Model assumptions will be investigated, and a suitable data transformation or non-parametric equivalent model substituted if appropriate.

Actual p-values and 95% confidence intervals for least square mean estimates of the treatment effects (including differences between active treatment and placebo) will be presented for these models.

7.1.3 Presentation

The summary statistics, including least squares mean estimates, 95% confidence interval and p-values will be presented using SAS output delivered in Word format.

7.2 Secondary Endpoints

7.2.1 Definitions

- Relative Change in UDysRS total score, calculated from baseline.
- Change in Total Objective Score (III, IV) of the UDysRS from Baseline (Day 1) to Visit 4 (Day 28).
- Change in total daily "OFF" time as assessed by patient completed 24-hour diaries, from run-in to Visit 4 (Day 28).
- Change in Unified Parkinson's Disease Rating Scale (MDS-UPDRS) sum score of parts II+ III (M-EDL+ ME)).
- Change in sum score of Questions 4.1 and 4.2 (dyskinesia) in MDS-UPDRS part IV to Visit 4 (Day 28).

Scale	Component	Attribute
UDysRS	Total Objective Score (III, IV)	Total score
MDS-UPDRS	Part II+III (M-EDL +ME)	Sum score
	Part IV Questions 4.1 and 4.2	Sum score
24-hour patient diaries	OFF time	Total daily hours

7.2.2 Analyses

The change from baseline will be defined as both absolute and percent change.

All Secondary endpoints can be considered quantitative continuous data (Interval in type). As such the Change from baseline to End of Treatment (Visit 4, Day 28 or earlier in the event of withdrawal) will be derived for each patient and analysed using an Analysis of Covariance (ANCOVA) model to compare the two treatment groups (IRL790 vs Placebo).

The ANCOVA analysis will allow estimation of the size of treatment effects as well as magnitude of differences between the active treatment and control (IRL790 - Placebo). The dependent variable will be the Change from baseline value and Treatment group the explanatory (independent) variable and fixed factor. A baseline covariate term will be included to ensure minimum variance unbiased estimation.

Model assumptions will be investigated, and a suitable data transformation or non-parametric equivalent model substituted if appropriate.

Actual p-values and 95% confidence intervals for least square mean estimates of the treatment effects (including differences between active treatment and placebo) will be presented for these models.

7.2.3 Presentation

The summary statistics, 95% confidence interval and p-values will be presented using SAS output delivered in Word format.

7.3 Exploratory Endpoints

7.3.1 Definitions

- Unified Parkinson's Disease Rating Scale (MDS-UPDRS), part I (total score), part II (total score), part III (total score) and part IV (total score) from Baseline (Day 1) to Visit 4 (Day 28).
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Question 1.2 (Hallucinations and Psychosis) from Baseline (Day 1) to Visit 4 (Day 28).
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Question 1.6 (Features of dopamine dysregulation syndrome) from Baseline (Day 1) to Visit 4 (Day 28).
    - Change in sum score of Questions 4.3, 4.4 and 4.5 (motor fluctuations) in MDS-UPDRS part IV to Visit 4 (Day 28).
    - Change in sum score of Questions 3.15 and 3.16 (postural and kinetic tremor of the hands) in MDS-UPDRS part III to Visit 4 (Day 28).
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Question 4.3 (Time spent in the off state) from Baseline (Day 1) to Visit 4 (Day 28).
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Question 4.6 (Painful off state dystonia) from Baseline (Day 1) to Visit 4 (Day 28).
- Clinician's Global Impression of Change in overall PD symptoms at Visit 4 (Day 28).
- Change in ”ON” time with troublesome dyskinesia as assessed by patient completed 24-hour diaries, from run-in to Visit 4 (Day 28).
- Change in ”ON” time as assessed by patient completed 24-hour diaries, from run-in to Visit 4 (Day 28).
- Change in Sleep time as assessed by patient completed 24-hour diaries, from run-in to Visit 4 (Day 28).

The change from baseline will be defined as both absolute and percent change.

7.3.2 Analyses

The Exploratory endpoints (except CGI) can be considered quantitative continuous data (Interval in type). As such the Change from baseline to End of Treatment (Visit 4, Day 28 or earlier in the event of withdrawal) will be derived for each patient and analysed using an Analysis Of Covariance (ANCOVA) model to compare the two treatment groups (IRL790 vs Placebo).

The ANCOVA analysis will allow estimation of the size of treatment effects as well as magnitude of differences between the active treatment and control (IRL790 - Placebo). The dependent variable will be the Change from baseline value and Treatment group the explanatory (independent) variable and fixed factor. A baseline covariate term will be included to ensure minimum variance unbiased estimation.

Model assumptions will be investigated, and a suitable data transformation or non-parametric equivalent model substituted if appropriate.

Actual p-values and 95% confidence intervals for least square mean estimates of the treatment effects (including differences between active treatment and placebo) will be presented for these models.

The CGI will be analysed using Chi-square test without continuity correction.

7.3.3 Presentation

The summary statistics, 95% confidence interval and p-values will be presented using SAS output delivered in Word format.

7.4 PK Endpoints

Plasma concentrations of IRL790 and its metabolites IRL872 and IRL 902 in samples obtained pre-dose and 2h post dose (Cmax) on Day 1 and Day 28 will be summarized, as interval data (using number (n), arithmetic mean, standard deviation (SD), minimum and maximum value, median, geometric mean and coefficient of variation (CV%)) by Day and time-point. If appropriate these will be presented overall for the IRL790 treated group but also according to IRL dose.

7.4.1 Definitions

All absolute and percent change in plasma concentration will be calculated as 2 hour value – pre-dose value.

7.4.2 Analyses

The absolute and percent change will be analyzed using Wilcoxon Rank Sum test.

7.4.3 Presentation

The summary statistics will be presented using SAS output delivered in Word format.

7.5 Safety Endpoints

7.5.1 Physical Examinations

Physical examination results will be categorically summarised as the number and percentage of patients according to treatment group and assessment day.

7.5.2 Vital signs

For blood pressure and pulse rate, Actual values and Change from Screening will be summarized with descriptive statistics, by treatment group and assessment day. Categorically classified (Normal/Abnormal) results will also be summarized.

In addition, Weight measured at Follow up following Screening will be summarised with descriptive statistics for Actual values and Change from Screening by treatment group.

7.5.3 ECG (12-Lead) At Rest

ECG variables will be summarised according to Actual values and Change from Screening using summary statistics and will be presented by treatment group and assessment visit. Categorically classified (Normal/Abnormal) results will also be summarised.

7.5.4 Safety laboratory

All haematology, clinical chemistry and coagulation laboratory tests will be summarised using listings for Actual values and Change from Screening and presented by treatment group and assessment day for each Hospital site separately (due to assays performed locally).

Additionally, the local laboratory normal ranges will be used to classify the results as: High, Normal or Low and categorical summaries presented overall according to treatment group and assessment visit. Pooling across all sites is possible here due to the categorical classification.

7.5.5 Adverse events

All AEs will be summarised according to TEAE or Baseline Event following classification of the verbatim terms according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The number and percentage of patients for all classified events will be presented according to System organ class (SOC) and Preferred term (PT) by treatment group and overall.

Separate summaries will be presented for all AEs by event frequency of occurrence and also for all AEs according to Seriousness, Severity and Relationship.

If appropriate separate summaries according to IRL790 maximum tolerated dose received may be used to support the findings.

7.6 Discontinuation

Patients who discontinue from IMP treatment will be tabulated. The reason for discontinuation will be given. For discontinuation due to AE, the AEs will be given.

7.7 Interim Analysis

Not applicable.

8 CHANGES FROM THE CSP

Clinician's Global Impression of Change in overall PD symptoms is assessed at Visit 4 (Day 28) only, and there is hence no comparison from baseline (Day 1) to Visit 4 (Day 28) as stated in the Clinical Study Protocol..

Change in total score of MDS-UPDRS part II+III has been included as a secondary endpoint.

Change in total score of MDS-UPDRS part II, and change in total score of UPDRS part III, have been added as exploratory endpoints.

9 STATISTICAL DELIVERABLES

The following documents will be delivered:

- SAP
- Statistical analyses, summary tables and listings

10 SOFTWARE

All statistical analyses will be performed using SAS Version 9.4 (SAS institute, Cary, NC).

11 APPROVAL

Issued by:

_____ _____

[redacted]

CTC Representative

Date (dd-Mmm-yyyy)

Approved by:

_____ _____

Sponsor Representative

Date (dd-Mmm-yyyy)

12 Appendix

12.1 Generic tables

Table 12.1-1 Generic table for categorical data

					XXXX	XXX
Category of Question		Assessment	Visit Name	Result		
XXX	YYY		Visit 8 Day 29	2. MUCH IMPROVED	0	1(17%)/6
				3. MINIMALLY IMPROVED	5(22%)/23	1(17%)/6
				4. NO CHANGE	11(48%)/23	4(67%)/6
				5. MINIMAL WORSENING	4(17%)/23	0
				6. MODERATE WORSENING	3(13%)/23	0

Table 12.1-2 Generic table for continuous data measured at one occasion

		XXXXX(N=25)	XXXXXX (N=7)	Total (N=32)
Age (years)	n/nmiss	25/0	7/0	32/0
	Mean (SD)	71.8 (3.89)	72.7 (5.59)	72 (4.23)

Table 12.1-3 Generic table for continuous data measured at several occasions

						XXX	XXX
Category of Question	Subcategory for Question	Assessment	Result Category	Visit Name			
A	C	C	Measured value	Visit 2 Day 1	N	23	6
					Mean (SD)	5.7 (1.7)	5.8 (2.4)
					Median (Min, Max)	5.0 (3, 10)	6.5 (3, 9)
					95% CI	5.0;6.5	3.3;8.4
				Visit 7 Day 28	N	23	6
					Mean (SD)	5.2 (2.1)	5.0 (3.0)
					Median (Min, Max)	5.0 (2, 9)	5.0 (2, 9)
					95% CI	4.3;6.1	1.8;8.2
			Absolute change from pre-dose baseline	Visit 7 Day 28	N	23	6
					Mean (SD)	-0.6 (2.0)	-0.8 (1.6)
					Median (Min, Max)	-1.0 (-5, 4)	0.0 (-4, 0)
					95% CI	-1.4;0.3	-2.5;0.8
					Within group p-value	0.1835	0.5000
			Relative change from pre-dose baseline (%)	Visit 7 Day 28	N	23	6
					Mean (SD)	-5.5 (42.8)	-16.7 (28.0)
					Median (Min, Max)	-10.0 (-71, 100)	0.0 (-67, 0)
					95% CI	-24.0;13.0	-46.0;12.7
					Within group p-value	0.2498	0.5000

12.2 AE tables

TABLE 14.3.1.1 OVERVIEW OF ADVERSE EVENTS, FAS

	XXXX N=31		XXXX N=32		Total N=32	
	n(%)	m	n(%)	m	n(%)	m
Any AE	12(39%)	17	10(31%)	16	16(50%)	33
Any SAE	0	0	0	0	0	0
Any AE leading to withdrawal	0	0	0	0	0	0
Any AE leading to death	0	0	0	0	0	0
Causality						
Not Related	8(26%)	9	5(16%)	8	9(28%)	17
Possibly Related	7(23%)	7	5(16%)	7	10(31%)	14
Probably Related	1(3%)	1	1(3%)	1	2(6%)	2
Severity						
Mild	9(29%)	11	8(25%)	9	13(41%)	20
Moderate	5(16%)	6	6(19%)	7	9(28%)	13

n, number of subjects; m, number of events
Percentages are based on the number of subjects in the full analysis set
XXXXXX.rtf AE: Overview of AEs, SAS program: ae_summary_tables.sas. Run by: XXXXXXX

TABLE 14.3.1.2 ADVERSE EVENTS BY SYSTEM ORGAN CLASS AND PREFERRED TERM, FAS

	XXXXXXX N=31		XXXXXXX N=32		Total N=32	
System organ class Preferred term	n(%)	m	n(%)	m	n(%)	m
Nervous system disorders	8(26%)	9	7(22%)	8	11(34%)	17
Headache	5(16%)	6	6(19%)	7	8(25%)	13
Paraesthesia	1(3%)	1	1(3%)	1	1(3%)	2
Presyncope	2(6%)	2	0	0	2(6%)	2
Gastrointestinal disorders	2(6%)	2	3(9%)	3	4(13%)	5
Nausea	2(6%)	2	2(6%)	2	3(9%)	4
Paraesthesia oral	0	0	1(3%)	1	1(3%)	1
General disorders and administration site conditions	1(3%)	1	2(6%)	2	3(9%)	3
Fatigue	1(3%)	1	2(6%)	2	3(9%)	3
Infections and infestations	2(6%)	2	1(3%)	1	3(9%)	3
Nasopharyngitis	2(6%)	2	1(3%)	1	3(9%)	3
Respiratory, thoracic and mediastinal disorders	2(6%)	2	1(3%)	1	2(6%)	3
Oropharyngeal pain	1(3%)	1	0	0	1(3%)	1
Rhinitis allergic	1(3%)	1	1(3%)	1	1(3%)	2
Musculoskeletal and connective tissue disorders	0	0	1(3%)	1	1(3%)	1
Back pain	0	0	1(3%)	1	1(3%)	1
Reproductive system and breast disorders	1(3%)	1	0	0	1(3%)	1
Dysmenorrhoea	1(3%)	1	0	0	1(3%)	1

TABLE 14.3.1.3 ADVERSE EVENTS: NUMBER OBSERVED AND RATE, WITH PATIENT IDENTIFICATIONS, FAS

			Mild --- NR	Mild --- Related	Moderate --- NR	Moderate --- Related	Total --- NR	Total --- Related	Total --- R+NR
XXXXXXX (N=32)	Gastrointestinal disorders	Nausea	1 (3%)	1 (3%)			1 (3%)	1 (3%)	2 (6%)
			106 **	108					
		Paraesthesia oral	1 (3%)				1 (3%)		1 (3%)
			127						
	General disorders and administration site conditions	Fatigue		1 (3%)		1 (3%)		2 (6%)	2 (6%)
				122		126			
	Infections and infestations	Nasopharyngitis	1 (3%)				1 (3%)		1 (3%)
			103						
	Musculoskeletal and connective tissue disorders	Back pain			1 (3%)		1 (3%)		1 (3%)
					103				
	Nervous system disorders	Headache	1 (3%)	2 (6%)	2 (6%)	1 (3%)	3 (9%)	3 (9%)	6 (19%)
			124	127 132	106 125	122			
		Paraesthesia		1 (3%)				1 (3%)	1 (3%)
				121					
	Respiratory, thoracic and mediastinal disorders	Rhinitis allergic			1 (3%)		1 (3%)		1 (3%)
					127				
XXXXXXXX (N=31)	Gastrointestinal disorders	Nausea		2 (6%)				2 (6%)	2 (6%)
				106 124					
	General disorders and administration site conditions	Fatigue				1 (3%)		1 (3%)	1 (3%)
						125			

		Mild --- NR	Mild --- Related	Moderate --- NR	Moderate --- Related	Total --- NR	Total --- Related	Total --- R+NR
Infections and infestations	Nasopharyngitis	2 (6%)				2 (6%)		2 (6%)
		116 125						
Nervous system disorders	Headache	2 (6%)	2 (6%)	1 (3%)		3 (10%)	2 (6%)	5 (16%)
		124 130	104 127	106				
	Paraesthesia		1 (3%)				1 (3%)	1 (3%)
			121					
	Presyncope				2 (6%)		2 (6%)	2 (6%)
					115 123			
Reproductive system and breast disorders	Dysmenorrhoea			1 (3%)		1 (3%)		1 (3%)
				114				
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	1 (3%)				1 (3%)		1 (3%)
		126						
	Rhinitis allergic	1 (3%)				1 (3%)		1 (3%)
		127						

**: Subject randomization number

AEs judged as 'Possibly Related' or 'Problably Related' are grouped as 'Related'.

XXXXXX.rtf AE: Number observed and rate, with patient identifications, FAS, SAS program: ae_tabulations.sas. Run by: XXXXX