Statistical Analysis Plan Update

Incidence of squamous cell carcinoma and other skin neoplasia in subjects with actinic keratosis treated with ingenol disoxate gel 0.018% or 0.037% or vehicle

Phase 3

A multi-centre, randomised, open-label, controlled, parallel group, 24-month trial

LEO Pharma A/S	**Trial ID:**	**LP0084-1369**
	Date:	**27-May-2018**
	Version:	**1.0**

This document has been redacted using the following principles: Where necessary, information is anonymised to protect the privacy of trial participants and named personnel associated with the trial as well as to retain commercial confidential information.
Summary data are included but data on individual trial participants, including data listings, are removed. This may result in page numbers not being consecutively numbered.
Appendices to the clinical trial report are omitted.
Further details and principles for anonymisation are available in the document LEO PHARMA PRINCIPLES FOR ANONYMISATION OF CLINICAL TRIAL DATA

1 Statistical Analysis Plan Approval

1.1 Approval Statement

On behalf of LEO, the Biostatistics Lead and the Medical Lead, are authorised to approve the Statistical Analysis Plan.

The QC statistician has by approving this document confirmed that the statistical information has been subject to statistical quality control.

The following persons have approved this Statistical Analysis Plan using electronic signatures as presented on the last page of this document.

PPD

Biostatistics Lead, Global Clinical Operations

PPD

Medical Lead, Medical Science and Safety

PPD

QC Statistician, Biostatistics

2 Statistical Analysis Plan Statements

2.1 Compliance with Good Clinical Practice

This Statistical Analysis Plan is designed to comply with the standards issued by the International Conference on Harmonisation (ICH) (E3: Structure and Content of Clinical Study Reports, E6: Good Clinical Practice, and E9: Statistical Principles for Clinical Trials).

Table of Contents

3 List of Abbreviations

3.1 List of Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AK	Actinic Keratosis
CTP	Clinical Trial Protocol
FAS	Full Analysis Set
FUAS	Follow-up Analysis Set
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
MedDRA	Medical Dictionary for Regulatory Activities
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma
SMQ	Standardised MedDRA Query
SOC	System Organ Class

4 Statistical Analysis Plan Authors

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5 Introduction

The statistical analysis will be performed as outlined in the Clinical Trial Protocol including amendments. This Statistical Analysis Plan contains a more technical and detailed elaboration of some points in the statistical analysis described in the Clinical Trial Protocol. Minor

deviations from the planned data presentation and analysis are accounted for. Furthermore, the analysis sets, which are to be used for the statistical analysis, are presented.

The original protocol was dated 23-Feb-2017 and a protocol amendment was issued 25-Jul-2017. Section 6.3 of the protocol was updated to include how sample size was determined for 1369. Section 11.1 was updated to include a precision estimate of the 3-year plus 2 month event rate of squamous cell carcinoma (SCC) where the 95% upper confidence limits are presented. Section 11.2 was updated to change the definition of the full analysis set from all enrolled and eligible subjects in 1369 to all randomized subjects from the pivotal phase 3 trials (LP0084-1193, -1194, -1195, -1196). Sections 11.3.4 and 11.3.5 were updated to include text specifying their respective null hypotheses. The remaining changes were either administrative or matters that needed further clarification. The change to section 11.2 has an impact on the data selection for the primary and secondary analyses, but does not change the manner in which the analyses are conducted. LEO Pharma decided to stop the trial prematurely and hence less data than expected were collected and analyzed.

6 Trial Analysis Sets

The analysis sets are determined based on the criteria defined in the Clinical Trial Protocol, which was changed from the original protocol dated 23-Feb-2017 to an amended version dated 25-Jul-2017. The analysis sets are defined as in the 4 main trials, and therefore a classification meeting will not take place for this trial.

6.1 Subjects enrolled in to LP0084-1369

A total of 562 subjects consented to and were enrolled into the extension trial LP0084-1369.

6.2 Full Analysis Set

A total of 1243 subjects were randomized in the 4 main trials. A total of 9 subjects withdrew consent prior to first application of investigational medicinal product (IMP). IMP was handed out to all 9 subjects but they returned the IMP unused. For all 9 subjects the decision to withdraw could therefore not have been biased by knowledge of the assigned treatment. The 9 subjects were excluded from the full analysis set (FAS) in alignment with ICH E9.

The remaining 1234 randomized subjects applied IMP and were included in the FAS.

6.3 Safety Analysis Set

All 1234 subjects in the FAS applied at least one dose of IMP and had presence or confirmed absence of adverse events (AEs) and thereby had post-baseline safety evaluations available. All 1234 subjects in the FAS are included in the safety analysis set.

6.4 Follow-up Analysis Set

The follow-up analysis set (FUAS) was defined as subjects in the FAS who were still in one of the main trials at visit 7 (week 8) and/or for whom evaluations after visit 7 (week 8) were available. The FUAS consists of 1172 subjects.

A difference between actual and planned treatment was only observed for 1 subject in FAS. The planned treatment was vehicle but the subject was treated with Ingenol Disoxate. The subject was included in FUAS but did not experience an event of SCC or other skin neoplasia.

7 Statistical Analysis

7.1 Baseline Considerations

7.1.1 Demographics

Demographics will be tabulated for the FAS as well as for subjects enrolled in LP0084-1369. Data will be presented by treatment location (face/chest or scalp) and treatment group within treatment location as well as overall by treatment group (ingenol disoxate versus vehicle). The protocol states that demographics will be presented by treatment group in the main trials and by country. However, from the analysis of the main trials it was found that treatment location is an important factor and therefore it was decided to present data by treatment group and location instead of by country. The demographic data, including age, from the time of randomization will be used. The analyses of demographics will be based on the planned treatment.

7.2 Analysis of Efficacy

The primary endpoint is time to first SCC in the treatment area. The event of an SCC is defined as AEs coded to the preferred term “Squamous cell carcinoma of skin” (MedDRA v. 18.1). The secondary time-to-event endpoint is time to first SCC or other skin neoplasia in the treatment area. The event of an SCC or other skin neoplasia is defined as AEs coded to preferred terms that are included in the standardised MedDRA query (SMQ) “Skin

malignancies" (MedDRA v. 18.1). The analyses of efficacy endpoints will be based on the planned treatment.

7.2.1 Primary Efficacy Criterion

The primary endpoint will be analysed as described in the clinical trial protocol (CTP).

The proportional hazards model will include planned treatment as explanatory variable, and have the proportional hazards assumptions checked by assessing whether or not the survival functions cross each other. The hazard ratio and corresponding 95% Wald confidence limits will be estimated within the proportional hazards model with planned treatment group as explanatory variable. A likelihood ratio test within the proportional hazards model will be applied for comparison of treatment groups. The results will be presented by treatment location (face/chest or scalp) and treatment group within treatment location as well as overall by treatment group (ingenol disoxate versus vehicle). The analysis will be based on the FAS.

The cumulative incidence rate will be calculated as the number of subjects with one or more events divided by the total observation period across all subjects in the FAS. The lower and upper limits of the 95% confidence interval will be calculated using the following SAS code:

Lower=((cinv(0.025,#subjects*2)/2)/total_obs_period)

Upper = ((cinv(0.975,2*(#subjects+1))/2)/total_obs_period)

The cumulative incidence rate and corresponding 95% confidence interval will also be presented by treatment location (face/chest or scalp) and treatment group within treatment location as well as overall by treatment group (ingenol disoxate versus vehicle).

For the landmark analysis described in the CTP time=0 will be defined as the date of visit 7 (week 8). This analysis will be based on the follow-up analysis set (FUAS) excluding subjects who experience an event prior to visit 7. Subjects in FUAS who do not have a visit 7, will have the date of their visit 7 imputed as the date of their visit 6 (week 4) plus 28 days.

7.2.2 Secondary Efficacy Criteria

The secondary endpoint will be analysed as described in the CTP and above for the primary endpoint.

7.3 Analysis of Safety

7.3.1 Adverse Events

AEs will be analysed as described in the CTP. AE tables will show the number of subjects and events. When counting the number of events multiple occurrences of the same preferred term within a subject will be counted as multiple events. Due to the premature stop of the trial no statistical testing will be performed for AEs. The CTP specified that serious adverse events (SAEs) occurring outside the treatment areas and considered not related to IMP in the main trials, should not be collected. Sporadically reported SAEs outside treatment area will therefore be removed from the ADaM datasets, but will appear in the SDTM datasets and the listing.

AEs that were ongoing at the end of the main trials were re-entered in the LP0084-1369 database for subjects enrolled in LP0084-1369, and these events were marked in the SDTM domain SUPPAE as such. A total of 69 AEs were re-entered in the LP0084-1369 database. The corresponding AEs in the main trials were identified by merging by subject, reported term and start date. In the 4 cases where the AEs in the main trials could not be identified by merging a manual review was performed to identify the corresponding AEs in the main trials. In cases of duplicate AEs only the AEs recorded in LP0084-1369 were included in the ADaM dataset. The analyses of AEs will be based on the actual treatment.

7.3.2 Scarring

Scarring will be presented in shift tables for the safety analysis set as well as for the set of subjects enrolled into trial LP0084-1369. All data on scarring collected in the 4 main trials and in trial LP0084-1369 will be included in the shift tables. The analyses of scarring will be based on the actual treatment.

7.3.3 Concomitant medication

Concomitant medication will be tabulated by ATC4 code and WHO dictionary derived term for subjects enrolled into trial LP0084-1369. Only concomitant medications registered in trial LP0084-1369 will be included. The analyses of concomitant medication will be based on the actual treatment.

7.4 General Principles

7.4.1 Handling of Drop-outs and Missing Values

Relatively few subjects in the FAS are expected to experience an event of SCC or other skin neoplasia, and therefore the amount of censoring in the analyses of the primary and secondary endpoints is expected to be substantial. All subjects who completed the 4 main trials without a prior event of SCC or other skin neoplasia and choose not to participate in the extension trial will be censored at the time they complete the main trial. All discontinued subjects without a prior event of SCC or other skin neoplasia will be censored at the time of discontinuation from the trial. The survival analyses performed will be evaluated in the presence of censoring.

7.4.2 Treatment Labels

In general, the results will be presented by treatment location (face/chest or scalp) and treatment group within treatment location as well as overall by treatment group (ingenol disoxate versus vehicle). The following treatment labels will be used: 0.018%, 0.037%, Ingenol disoxate and Vehicle.

Appendix I

Tables

- Analysis of time to first SCC in the treatment area from Visit 2 in trials LP0084-1193, -1194, -1195 and -1196: full analysis set
- Analysis of time to first SCC or other skin neoplasia in the treatment area from Visit 2 in trials LP0084-1193, -1194, -1195 and -1196: full analysis set
- Analysis of time to first SCC in the treatment area from Visit 7 in trials LP0084-1193, -1194, -1195 and -1196: full analysis set
- Analysis of time to first SCC or other skin neoplasia in the treatment area from Visit 7 in trials LP0084-1193, -1194, -1195 and -1196: full analysis set

- Incidence of SCC in the treatment area from Visit 2 in trials LP0084-1193, -1194, -1195 and -1196: full analysis set
- Incidence of SCC or other skin neoplasia in the treatment area from Visit 2 in trials LP0084-1193, -1194, -1195 and -1196: full analysis set
- Incidence of SCC in the treatment area from Visit 7 in trials LP0084-1193, -1194, -1195 and -1196: full analysis set
- Incidence of SCC or other skin neoplasia in the treatment area from Visit 7 in trials LP0084-1193, -1194, -1195 and -1196: full analysis set

- Demographics: full analysis set
- Demographics: subjects enrolled in LP0084-1369

- Disposition: full analysis set
- Disposition: subjects enrolled in LP0084-1369

- Concomitant medication in LP0084-1369: subjects enrolled in LP0084-1369

- Scarring, shift table by visit (observed cases): safety analysis set
- Scarring, shift table by visit (observed cases): subjects enrolled in LP0084-1369

- Adverse events summary for LP0084-1369: subjects enrolled in LP0084-1369
- Adverse events summary (week 8 - months 14 in main trials and LP0084-1369): follow-up analysis set

- Adverse events by SOC and preferred term in LP0084-1369: subjects enrolled in LP0084-1369
- Adverse events by SOC and preferred term (week 8 - months 14 in main trials and LP0084-1369): follow-up analysis set

- Frequent adverse events (>= 2% in the active treatment group) by SOC and preferred term in LP0084-1369: subjects enrolled in LP0084-1369
- Frequent adverse events (>= 2% in the active treatment group) by SOC and preferred term (week 8 - months 14 in main trials and LP0084-1369): follow-up analysis set

- Adverse events by severity, SOC and preferred term in LP0084-1369: subjects enrolled in LP0084-1369
- Adverse events by severity, SOC and preferred term (week 8 - months 14 in main trials and LP0084-1369): follow-up analysis set

- Related adverse events by SOC and preferred term in LP0084-1369: subjects enrolled in LP0084-1369
- Related adverse events by SOC and preferred term (week 8 - months 14 in main trials and LP0084-1369): follow-up analysis set

- Related adverse events by severity, SOC and preferred term in LP0084-1369: subjects enrolled in LP0084-1369
- Related adverse events by severity, SOC and preferred term (week 8 - months 14 in main trials and LP0084-1369): follow-up analysis set

- Serious adverse events by SOC and preferred term in LP0084-1369: subjects enrolled in LP0084-1369
- Serious adverse events by SOC and preferred term (week 8 - months 14 in main trials and LP0084-1369): follow-up analysis set
- Serious adverse events by causal relationship, SOC and preferred term in LP0084-1369: subjects enrolled in LP0084-1369
- Serious adverse events by causal relationship, SOC and preferred term (week 8 - months 14 in main trials and LP0084-1369): follow-up analysis set

- SCC or other skin neoplasia inside treatment area by lowest level term in LP0084-1369: subjects enrolled in LP0084-1369
- SCC or other skin neoplasia inside treatment area by lowest level term (week 8 - months 14 in main trials and LP0084-1369): follow-up analysis set

- SCC or other skin neoplasia (consolidated terms) inside treatment area by preferred term in LP0084-1369: subjects enrolled in LP0084-1369
- SCC or other skin neoplasia (consolidated terms) inside treatment area by preferred term (week 8 - months 14 in main trials and LP0084-1369): follow-up analysis set

- Non-serious adverse events by SOC and preferred term in LP0084-1369: subjects enrolled in LP0084-1369
- Non-serious adverse events by SOC and preferred term (week 8 - months 14 in main trials and LP0084-1369): follow-up analysis set

- Adverse events leading to withdrawal by SOC and preferred term in LP0084-1369: subjects enrolled in LP0084-1369
- Adverse events leading to withdrawal by SOC and preferred term (week 8 - months 14 in main trials and LP0084-1369): follow-up analysis set

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- Kaplan-Meier curve for SCC (face/chest): full analysis set
- Kaplan-Meier curve for SCC (landmark analysis, face/chest): follow-up analysis set
- Kaplan-Meier curve for SCC (scalp): full analysis set
- Kaplan-Meier curve for SCC (landmark analysis, scalp): follow-up analysis set
- Kaplan-Meier curve for SCC: full analysis set
- Kaplan-Meier curve for SCC (landmark analysis): follow-up analysis set
- Kaplan-Meier curve for SCC or other skin neoplasia (face/chest): full analysis set
- Kaplan-Meier curve for SCC or other skin neoplasia (landmark analysis, face/chest): follow-up analysis set
- Kaplan-Meier curve for SCC or other skin neoplasia (scalp): full analysis set
- Kaplan-Meier curve for SCC or other skin neoplasia (landmark analysis, scalp): full analysis set

- Kaplan-Meier curve for SCC or other skin neoplasia: full analysis set
- Kaplan-Meier curve for SCC or other skin neoplasia (landmark analysis): follow-up analysis set
- Onset of each SCC for face/chest (left panel) and scalp (right panel): follow-up analysis set
- Onset of each SCC or other skin neoplasia for face/chest (left panel) and scalp (right panel): follow-up analysis set

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- Serious adverse events (week 8 - months 14 in main trials and LP0084-1369): follow-up analysis set