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Clinical Trial Protocol Title:

A PHASE 3, MULTICENTRE, RANDOMISED, DOUBLE-BLIND, VEHICLE-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TIRBANIBULIN 10 MG/G OINTMEINT APPLIED TO A TREATMENT FIELD LARGER THAN 25 CM^2 AND UP TO 100 CM^2 IN ADULT PATIENTS WITH ACTINIC KERATOSIS

EU LARGE FIELD

Statistical Analysis Plan for Clinical Trial M-14867-33

PPD

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AK	Actinic Keratosis
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
CCI	CCI
CC	Complete clearance
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CRO	Clinical Research Organization
CSP	Clinical Study Protocol
eCRF	Electronic Case Report Form
e.g.	Example Given
EoS	End of Study
EoT	End of Treatment
ET	Early Termination
FWER	Familywise error rate
ICF	Informed Consent Form
i.e.	In other words
ITT	Intent-To-Treat population
LS	Least-squares
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
CCI	CCI
CCI	CCI
PC	Partial Clearance
PDF	Portable Document Format
PE	Physical Examination
Q1	First quartiles
Q3	Third quartiles
RD	Risk difference
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCC	Squamous cell carcinoma
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TF	Treatment Field
TFS	Trial Form Support
CCI	CCI
vs	Versus
WOCBP	Women of child-bearing potential
WHO	World Health Organization

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2. Introduction

This Statistical Analysis Plan (SAP) is based on CSP (clinical study protocol) Version 3.0, dated January 31, 2024.

This is a Phase 3, multicentre, randomised, double-blind, vehicle-controlled, parallel-group study to evaluate the efficacy and safety of tirbanibulin 10 mg/g ointment applied to a Treatment Field (TF) larger than 25 cm^2 and up to 100 cm^2 and containing 4 to 12 lesions, inclusive, in adult patients with Actinic Keratosis (AK).

The study consists of a 4-week Screening Period, a 4-month Treatment and Response Assessment Period (core study), and a 32-week Follow-Up Period. Study visits and assessments will be performed in accordance with the Schedule of Assessments (Table 1 for Screening Period and Treatment and Response Assessment Period, and Table 2 for Follow-Up Period).

Approximately 270 patients will be enrolled in the study. Enrolment will be controlled so that approximately two-thirds of enrolled patients will be treated on the face and approximately one-third of enrolled patients will be treated on the scalp Further, at least 25% of the patients will have an affected field of approximately 100 cm^2.

At Day 1/Baseline, eligible patients will be randomised in a 2:1 ratio to either tirbanibulin 10mg/g ointment or vehicle CCI the randomisation will be stratified by the number of lesions at baseline (≥4 to ≤8, >8 to ≤12), treatment location (face or balding scalp), and country. If a limited number of patients is anticipated to be enrolled within a specific country, that country may be combined with another country in the stratification.

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The Sponsor, Contract Research Organization (CRO) and vendors involved in the conduct of the trial, the Investigators, trial site personnel, and patients will be blinded to the treatment assigned to each patient.

During the Treatment and Response Assessment Period, patients will apply study drug (tirbanibulin 10 mg/g ointment or vehicle) once daily for 5 days beginning on Day 1. All patients will be evaluated for efficacy, safety, and tolerability at Days 8, 15, 29, and 57.

Those patients who do not achieve complete clearance (CC) at Day 57 will receive a second 5-day course of the randomised treatment. Patients receiving a second treatment course will also be evaluated for efficacy, safety, and tolerability at Days 64, 71, and 85.All patients, regardless of whether

they receive one or two treatment courses, will have a final evaluation at Day 113.

Patients who achieve CC (no lesions in the treatment field at either Day 57 or Day 113) will be able to continue the study in the 32-week Follow-up Period and will have the opportunity to receive treatment courses with tirbanibulin 10 mg/g ointment, as needed, during this period CCI .

The first Follow-Up Period visit (FUP1) will coincide with the Day 113 core study visit. Patients who have lesions in the treatment field at FUP1 will receive a course of tirbanibulin 10 mg/g ointment CCI CCI if at least 16 weeks have elapsed since starting the most recent treatment course (ie, patients who received just 1 treatment course during the core study); otherwise, physical treatments should be administered. Follow-Up Period visit 2 (FUP2) will occur 16 weeks after FUP1. Patients with lesions in the treatment field at FUP2 will receive a course of tirbanibulin 10 mg/g ointment.

Patients who do not achieve CC at either Day 57 or Day 113 will not be treated with study drug during the Follow-Up Period and will only undergo safety assessments (AEs and concomitant medications) CCI . No site visits are required, and safety data collection will be done remotely (ie, by telephone or other means) (Table 2). During the Follow-Up Period, these patients may receive standard of care treatment, as per the discretion of their treating physician.

All patients will have a final visit or telephone contact at Week 48.

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Table 1 Schedule of Assessments – Screening Period and Treatment and Response Assessment Period

Period	Screening Period*	Treatment & Response Assessment Period										
		1st treatment course for all patients		Response Assessment			Response Assessment 2nd treatment course for non-CC patients		Response Assessment			
Visit	1	2	At home	3	4	5	6 EoT (CC patients)	At home	7[b]	8[b]	9[b]	10 ET / EoS
Day	-28 to -1	1 (Baseline)	2-5	8	15	29	57 (Week 8)	58-61	64	71	85	113 (Week 16)
Visit Time Window (days)	None	None		±2	±2	±2	±2		±2	±2	±2	±3
Informed consent	X											
Inclusion & exclusion criteria	X	X[a]										
Demographics	X											
Medical/surgical history	X											
AK history/AK treatment history	X											
Prior and concomitant medications/therapies	X	X[a]		X	X	X	X[g]		X	X	X	X
Fitzpatrick skin-type scale	X											
Treatment field identification[l]	X	X[a]										
Vital signs[m]	X	X[a]					X[g]					X
Physical examination[f]	X											X
Clinical chemistry and haematology	X											X
Pregnancy test for WOCBP[d]	X	X[a]					X[g]					X
Randomization		X										
Study App installation and instructions or diary dispensed[n]		X[a]										
Study drug application		X	X				X[e]	X[e]				
Instructions for self-administration and study drug dispensing		X					X[e]					
Study drug return				X					X[e]			
Patient diary review by Investigator[n]				X					X			
Treatment field location		X[a]	X	X	X	X	X	X[e]	X	X	X	X
AK lesion count in the TF	X	X[a,h]		X[o]	X[o]	X[o]	X[g,o]		X[o]	X[o]	X[o]	X[o]
Standardized photography	X	X[a,i]		X	X	X	X[g]		X	X	X	X
AEs[j]	X	X[a]		X	X	X	X[g,k]		X	X	X	X[k]

Period	Screening Period*	Treatment & Response Assessment Period										
		1st treatment course for all patients		Response Assessment			Response Assessment 2nd treatment course for non-CC patients		Response Assessment			
Visit	1	2	At home	3	4	5	6 EoT (CC patients)	At home	7[b]	8[b]	9[b]	10 ET / EoS
Day	-28 to -1	1 (Baseline)	2-5	8	15	29	57 (Week 8)	58-61	64	71	85	113 (Week 16)
Visit Time Window (days)	None	None		±2	±2	±2	±2		±2	±2	±2	±3
Focused dermatological exam of treatment field												
Local tolerability		X[a]		X	X	X	X[g,k]		X	X	X	X[k]
Hypo- and hyperpigmentation and scarring		X[a]		X	X	X	X[g,k]		X	X	X	X[k]
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Abbreviations: AE=adverse event, AK=Actinic Keratosis, CC=Complete Clearance, ET=Early Termination, EoT=End of Treatment, EoS=End of Study, ICF=informed consent form, TF=treatment field, CCI [redacted] WOCBP=women of child-bearing potential.

* Patients who require a washout period from prohibited medication longer than 4 weeks would be considered a screen failure and documented as such in the eCRF. The patient may be rescreened once..

[a] Assessments/procedures performed before randomization. Day 1 evaluation will serve as a Baseline for these assessments.

[b] Visits 7, 8, and 9 and associated assessments are applicable only for patients who receive a second treatment course with study drug.

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[d] Highly sensitive urinary pregnancy test performed at the clinical trial site. At Day 57, only for non-CC patients who are to be treated with a second course.

[e] Study drug application, instructions, and dispensing at Day 57, and study drug return at Day 64, are only for patients who receive a second treatment course with study drug.

[f] Physical examination to include height, weight, and an assessment of head, eyes, ears, nose and throat, integumentary/dermatological, gastrointestinal, cardiovascular, respiratory, musculoskeletal, and neurological systems. Height is measured only at screening. An expanded dermatological examination to cover the sun-exposed areas, where photo-damage is likely, will be conducted at Screening only.

[g] Assessments prior to dose administration.

[h] Olsen grade (1 or 2) of lesions in the TF will be assessed Day 1/Baseline, Day 57, and, for patients who receive a second course of treatment, Day 113.

[i] Baseline photo is only required in case of any significant change from Screening is detected in the TF as per the Investigator judgement or if the quality of the image captured at screening is not appropriate. If no photo is needed at baseline, then the Screening photo will be considered the baseline assessment.

[j] At each study visit, patients will be asked a general question "How have you been since the last visit?" AEs will be recorded before assessments of local tolerability, pigmentation, and scarring in the TF. AEs will be reported separately from local tolerability signs.

[k] All patients who have unresolved local tolerability signs, hypo- or hyperpigmentation, scarring in the TF, or treatment-related AEs at End of Treatment (Day 57 for CC pts and Day 113) will return for additional follow-up every 7 to 28 days until these have resolved, have returned to the baseline value, or are deemed stabilized by the Investigators.

[l] Treatment Field location (face/scalp) and measurement of the size at screening or baseline in case of non-valid measurement at screening.

[m] Measurement of vital signs will include blood pressure, heart rate, respiratory rate, and tympanic temperature. Measurements of systolic and diastolic blood pressure will be performed after at least 5 minutes of rest in a supine position and always using the same arm.

[n] Patients will complete a diary daily to record dates and times of study treatment application. The diary will be checked by the Investigator at the next visit scheduled after the study treatment course(s).

[o] AK lesion count will include the total number of lesions in the TF as well as separately the number of new lesions (i.e., not present at baseline).

[p] Only applicable to patients who receive a second course of treatment.

CCI [redacted]

Table 2 Schedule of Assessments – Follow-Up Period

Period	Long Term Follow-up Period				
Visit	**FUP1**	**At home**	**FUP2**	**At home**	**FUP3 ET/EoS**
Day	**113 (Week 16)**	**+4 days**	**225 (Week 32)**	**+4 days**	**337 (Week 48)**
Visit Time Window (days)	**±7**		**±7**		**±7**
Procedures and Assessments for Patients Who Achieved CC at Day 57 or 113 of the Core Study					
Informed consent signed[a]	X				
Concomitant medications/therapies			X		X
Vital signs[b]					X
Physical examination[c]					X
Clinical chemistry and haematology					X
Pregnancy test for WOCBP[d,g]			X		X
Study drug application[e]	X	X	X	X	
Instructions for self-administration and study drug dispensing[e]	X		X		
Study drug return[e]			X		X
Patient diary review by Investigator[j]			X		X
Treatment field location[g]		X	X	X	X
AK lesion count in the treatment field[g,f]			X[k]		X[k]
Standardized photography[g]			X		X
AEs[g,h]			X		X[i]
Procedures and Assessments for Patients Who Did Not Achieve CC at Day 57 or 113 of the Core Study[l]					
Informed consent signed[a]	X				
Concomitant medications/therapies			X		X
AEs[h]			X		X[i]
Site to contact patient by telephone or other means			X[h]		X[h]

Abbreviations: AE=adverse event, AK=Actinic Keratosis, CC=Complete Clearance, ET=Early Termination, EoS=End of Study, FUP=Follow-Up Period, ICF=informed consent form, TF=treatment field, WOCBP=women of child-bearing potential.

[a] All patients to sign a consent for enrolment in the Follow-Up Period.

[b] Measurement of vital signs will include blood pressure, heart rate, respiratory rate, and tympanic temperature. Measurements of systolic and diastolic blood pressure will be performed after at least 5 minutes of rest in supine position and always using the same arm.

[c] Physical examination to include weight, and an assessment of head, eyes, ears, nose and throat, integumentary/dermatological, gastrointestinal, cardiovascular, respiratory, musculoskeletal, and neurological systems.

[d] Highly sensitive urinary pregnancy test performed at the clinical trial site only for non-CC patients who are to be treated with a tirbanibulin course.

[e] Study drug application, instructions, and dispensing only for non-complete clearance patients who receive a tirbanibulin course.
[f] Olsen grade (1 or 2) of lesions in the TF will be assessed every visit.
[g] Assessments prior to dose administration.
[h] At each study visit (or telephone contact), patients will be asked a general question "How have you been since the last visit?"
[i] All patients who have unresolved treatment-related AEs will return for additional follow-up every 7 to 28 days until these have resolved, have returned to the baseline value, or are deemed stabilized by the Investigators.
[j] Patients will complete a diary to record dates and times of study treatment application. The diary will be checked by the Investigator at the next visit scheduled after the study treatment course(s).
[k] AK lesion count will include the total number of lesions in the TF as well as separately the number of new lesions (i.e., not present at baseline).
[l] No site visits are required per protocol and all data will be collected remotely.

3. Objectives, Endpoints and Estimands

3.1. Objectives and Endpoints

Primary objective:

- To assess the efficacy of tirbanibulin 10 mg/g ointment compared to vehicle on the clearance of AK lesions after 1 course of treatment at Day 57 (Week 8) in adults with AK on the face or scalp

Primary Endpoint:

- Percent change from baseline in lesion count at Day 57.

Key Secondary Endpoint:

- Proportion of patients with partial clearance (PC) at Day 57, defined as ≥75% clearance in the TF at Day 57.
- Proportion of patients with complete clearance (CC) at Day 57, defined as 100% clearance in the TF at Day 57.

Secondary objectives:

- To assess the efficacy of tirbanibulin 10 mg/g ointment compared to vehicle on the clearance of AK lesions after up to 2 courses of treatment at Day 113 (Week 16) in adults with AK on the face or scalp.

Key Secondary Endpoints:

- Proportion of patients with PC by Day 113, defined as 100% clearance in the TF at Day 57 or, for patients receiving a second treatment course, ≥75% clearance at Day 113.
- Proportion of patients with CC by Day 113, defined as 100% clearance in the TF at Day 57 or, for patients receiving a second treatment course, 100% clearance at Day 113.

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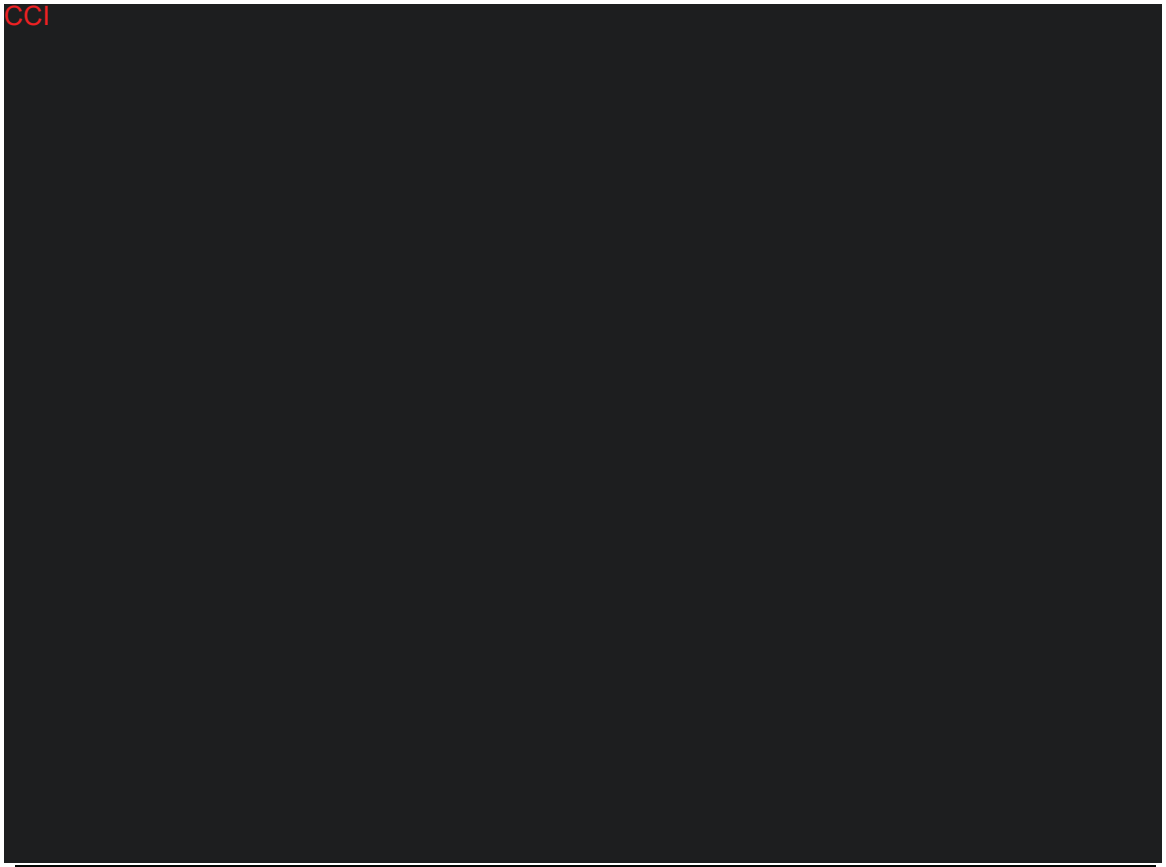

Safety Endpoints:

- Local tolerability score (0-3) by treatment course and visit for each individual sign.
- Maximum local tolerability score by treatment course for each individual sign.
- Time to the maximum local tolerability score is observed by treatment course for each individual sign.
- Local tolerability signs composite score (0-18) by treatment course and visit, defined as the sum of scores graded from 0 to 3 on all six individual tolerability sign categories.
- Maximum local tolerability signs composite score by treatment course.
- Time to the maximum local tolerability signs composite score is observed by treatment course.
- Change in pigmentation and scarring in the TF by treatment course and visit.
- AEs, SAEs, AESIs, abnormalities in clinical laboratory results and vital signs.

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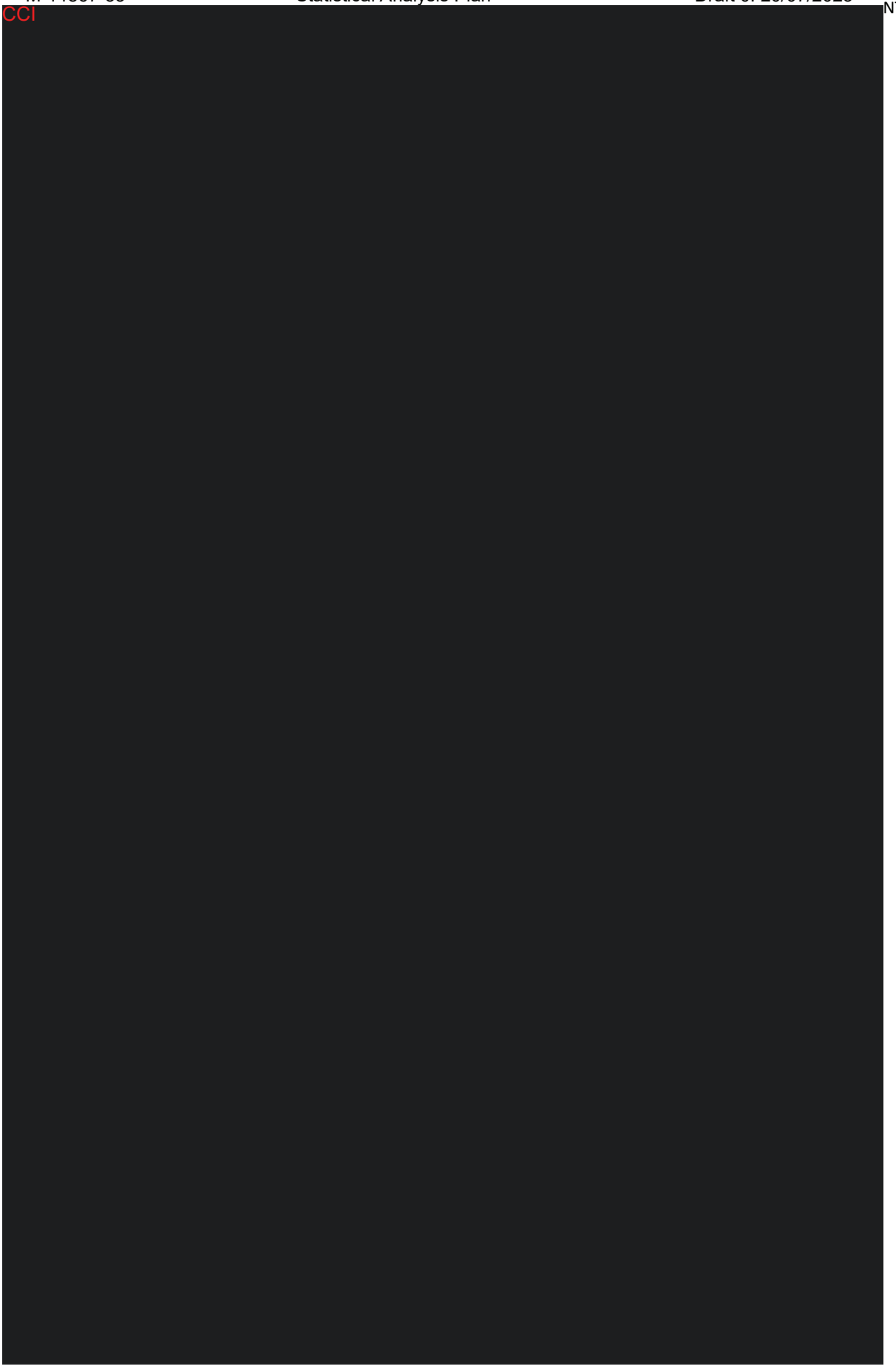

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5. Structure and methodology of statistical analysis

Statistical analyses of demographic, baseline characteristics, efficacy, safety and tolerability data will be performed by the CRO Biostatistics Department.

The Statistical Analysis System (SAS, version 9.4) will be the statistical software used to analyse the data sets.

Tables, figures, and listings will be compiled in the statistical report and appended to the Clinical Study Report. All tables, figures and listings will be presented in PDF documents without any manual editing, i.e. they will appear unmodified as programmed by means of the statistical package.

All variables will be analysed by means of descriptive statistics. Continuous variables will be summarized using the number of non-missing observations (n), number of missing observations, mean, standard deviation (SD), standard error (SE) of the mean, 95% CI of the mean, median, first (Q1) and third (Q3) quartiles, minimum (min) and maximum (max) value, as appropriate depending on analysis goals. Categorical variables will be summarised using the number of missing observations, frequency counts (n) and percentages (%).

6. Analysis populations

There will be four different analysis populations in the trial:

- Intention-To-Treat (ITT) population will comprise all randomized patients.
- Safety (SAF) population will comprise all randomized patients who received at least one application of study treatment during the core study.

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7. Patient disposition

The number of screened patients will be summarised. The number and percentage of screening failures and the associated reasons for failure will be tabulated.

The number of patients entering the trial and number and percentage of patients included in each trial population (ITT and Safety populations for the core study and Follow-Up Period) will be summarised.

The above summary will be presented overall, by each stratification factor and by combination of the 3 stratification factors.

Inclusion and exclusion criteria, recorded during the screening phase and during visit 2 (Baseline), will be described using descriptive statistics according to Section 5. Analyses of inclusion and exclusion criteria will be based on the screened patients.

The number and percentage of patients available at each visit will also be summarised. Visit disposition will be summarized using ITT.

The number and percentage of patients who complete the study and who prematurely discontinue their participation in the trial, as well as the reasons for the discontinuation as recorded on the End of Study (EOS) visit on the Electronic Case Report Form (eCRF), will be summarised. Similarly, the number and percentage of patients who complete the treatment and of those who prematurely discontinue the treatment but remain in the study, as well as the reasons for treatment discontinuation as recorded on the End of Treatment (EOT) form on the eCRF will be summarised by each treatment course. Study discontinuation will be summarized using ITT and treatment discontinuation will be summarized using the Safety populations for the core study and Follow-Up Period.

8. Demographic and other baseline (Screening) characteristics

Demographic and baseline characteristics will be analysed by means of descriptive statistics according to Section 5. No statistical tests will be performed for these variables.

Unless otherwise specified, the baseline value of each assessment will be defined as the latest non-missing value assessed before the first dose of study treatment.

Demographic characteristics to be assessed are age, sex, race and ethnicity.

Baseline characteristics to be assessed include:

- Medical/surgery history at screening.
- Smoking habits and alcohol consumption at screening.
- Fitzpatrick skin type at screening.
- Vital signs (systolic and diastolic blood pressure after at least 5 min resting in the supine position, heart rate, respiratory rate and tympanic temperature) at baseline.
- Urine pregnancy test for WOCBP at baseline.
- Physical examination at screening, including height, weight, and an assessment of head, eyes, ears, nose and throat, integumentary/dermatological, gastrointestinal, cardiovascular, respiratory, musculoskeletal, and neurological systems, and an expanded dermatological examination to cover sun-exposed areas where photo-damage is likely.
- Laboratory safety parameters (haematology and clinical chemistry) at screening.
- AK history at screening.
- TF location at baseline.
- TF size at baseline (>25-50 cm^2, >50-75 cm^2, >75-<100 cm^2 and 100 cm^2 *)
- Number of lesions inside the treatment field at baseline, presented by TF location (face or scalp) and overall.
- Number and percentage of patients with Olsen grade I lesions only, with Olsen grade II lesions only and with both types of lesions inside the TF at Baseline.
- Percentage of Olsen grade I and Olsen grade II lesions over the total number of lesions assessed at Baseline inside the TF.

All demographic and baseline characteristics will be analysed using the ITT.

Additionally, a table summarizing the demographic characteristics for the screening failures, will also be provided.

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* 100 cm includes +/- 10% range

10. Analyses of Prior and Concomitant Medication

Medications will be coded according to the World Health Organization Drug Dictionary (WHO-DD) C3 March 1, 2022.

Prior medications are defined as any medication started and discontinued prior to the first study treatment dosing. Concomitant medications are defined as any medication started on the same day than or after the first study treatment dosing, including those who started prior to the first study treatment date and continued past that date.

Incidence of prior and concomitant medications will be tabulated by anatomical therapeutic chemical (ATC) Level 3 and standardized drug name using the safety population. A patient with the same medication taken multiple times will be counted only once for the corresponding standardized drug name. Similarly, if a patient has taken more than one medication within the same ATC level, then the patient will be counted only once for that ATC. Prior and concomitant medications will be sorted alphabetically by ATC level and within each ATC level, the standardized drug name will be presented by decreasing order.

Prior and concomitant medication information will be presented in a by-patient listing using the Safety populations for the core study and Follow-Up Period.

11. Analyses of Efficacy Endpoints

All efficacy analysis will be performed on the ITT population.

11.1. Primary Endpoint

The primary endpoint is the percent change from baseline in lesion count at Day 57 (Week 8), and will be computed as follows:

$$\frac{\text{Number of lesions at Day 57} - \text{Number of lesions at Baseline}}{\text{Number of lesions at Baseline}} \times 100$$

This endpoint will be analysed by means of an analysis of covariance (ANCOVA) model using treatment group, treatment location, and country as factors, and baseline number of lesions as covariate.

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[redacted]

Least-squares (LS) mean of percent change from baseline and 95% CI will be present by treatment group. Between-treatment group LS mean difference and 95% CI will be presented overall.

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[redacted]

CCI [redacted]

11.2. Key Secondary Endpoints

The four key secondary efficacy endpoints, PC rate at Day 57 (Week 8), CC rate at Day 57 (Week 8), PC rate at Day 113 (Week 16), and CC rate at Day 113 (Week 16) will be analysed by treatment group using the Cochran-Mantel-Haenszel (CMH) method controlling for treatment location (face or scalp), baseline number of lesions (≤8 or >8), and country.

Clearance percentage (at patient level) will be calculated as follows:

$$\text{Clearance at Day } i = \frac{\text{Number of baseline lesions} - \text{Number of lesions at Day } i}{\text{Number of baseline lesions}} \times 100$$

Partial clearance will be considered when clearance is ≥75% (including also 100% clearance). Complete clearance will be considered when clearance is 100%.

Patients with missing data on AK lesion number at Week 8 for patients with 1 treatment course or at Week 16 for patients with 2 treatment courses will be considered failures for the binary endpoints at Week 8 and 16, respectively. Also, patients who permanently discontinued treatment will be considered as failures.

For the binary endpoints (PC and CC), CCI [redacted] and risk difference with 95% CIs will be presented together with the p-value of the CMH test. The 95% CI for the risk difference will also be presented using the Miettinen and Nurminen approach (Farrington 1990, Miettinen 1985).

The percentage of patients with PC and its 95% CI and the percentage of patients with CC and its 95% CI will be provided for each treatment group overall and for each treatment group by treatment location, baseline number of lesions (≤8 or >8) and country using Wilson's score method. The 95% CI for the difference in proportions of patient with success between treatment groups will also be presented for each treatment location, for each baseline number of lesions (≤8 or >8) and for each country using Newcombe confidence limits.

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12. Analyses of Safety Endpoints

Descriptive statistics will be provided for all safety endpoints. Safety analyses will be performed by treatment group and by the number of treatment courses applied (1 or 2) during the core study using the SAF. Safety analyses will be reported separately for the Follow-Up Period safety populations, CCI

12.1. Local tolerability

At each site visit, the Investigator will assess the local tolerability in the TF. The six local tolerability signs to be assessed and the corresponding grading scale for each sign are described in Table 4.

Local tolerability score for each individual sign and the local tolerability composite score, defined as the sum of scores graded from 0 to 3 on all six individual tolerability sign categories, will be analysed by means of descriptive statistics and provided by treatment group for Weeks 1 to 8 and, for those patients who received 2 courses, by treatment group for Weeks 1 to 16.

The maximum local tolerability score for each individual sign and the maximum local tolerability composite score will be presented by treatment group for Weeks 1 to 8 and, for those patients who received 2 courses, by treatment group for Weeks 8 to 16.

Time when the maximum local tolerability score for each individual sign and the maximum local tolerability composite score are observed will be described by treatment group for Weeks 1 to 8 and by number of courses received and treatment group for Weeks 1 to 16.

Local tolerability will only be assessed during the core study and using the SAF.

Table 4 Local Tolerability Signs and Grading Scale

Local Tolerability Sings	Local Tolerability Score
Erythema Flaking/scaling Crusting Swelling Vesiculation/pustulation Erosion/ulceration	0 = Absent 1 = Mild (slightly, barely perceptible) 2 = Moderate (distinct presence) 3 = Severe (marked, intense)

12.2. Pigmentation changes and scarring

The number and percentage of patients with hypo- or hyperpigmentation and scarring in the TF will be presented separately by treatment group for Weeks 1 to 8 and by number of courses received and treatment group for Weeks 1 to 16.

12.3. Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a clinical trial participant, regardless of the administration of the investigational medicinal product and its causal relationship to it.

An AE can therefore be any unfavourable and unintended medical occurrence during the patient's participation in the trial, including deterioration of a pre-existing medical condition, an abnormal value in a laboratory assessment, vital signs measure, or an abnormal finding in the physical examination.

Adverse events will be collected from signature of the informed consent form (ICF) up to Week 48/ET (for patients that in the Follow-up Period enter the CCI all AEs will be reported except AEs and abnormal values related to vital signs, physical examination and clinical laboratory since these data will not be collected for this group of patients). Any AE reported by the patient up to 30 days after the last study contact (Week 48/ET) should also be captured in the eCRF.

Only Treatment-emergent AEs (AEs that occurred after the first administration of the IMP, either Tirbanibulin or Vehicle, during the study) and SAEs will be included in the safety analysis.

Summary of AEs will be presented by patients with AEs, study drug-related AEs, AEs of Special Interest (AESIs), Severe AEs, Serious AEs (SAEs), AEs leading to temporary or definite discontinuation of the study treatment, AEs leading to study discontinuation and patients with fatal AEs.

The number and percentage of patients who experience one or more AEs, and the number of AEs episodes will be tabulated, by treatment group and overall, by:

- System organ class (SOC) term, and preferred term.
- SOC term, preferred term, and location (at or just around the TF: ≤2 cm from the application area; or distant: >2 cm from the TF).
- SOC term, preferred term, and severity (mild, moderate and severe).
- SOC term, preferred term, and causality (related, including 'Possibly related' and 'Related' classifications, or not related, including 'Unlikely related' and 'Not related').
- SOC term, preferred term, and seriousness (yes/no).
- SOC term, preferred term, and action taken (drug withdrawn, dose not changed or not applicable).
- SOC term, preferred term, and outcome (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, Not recovered/not resolved, fatal, unknown).

In the event of one episode of an AE (continuous in time) with multiple intensities being reported by the same patient, the maximum severity (severe > moderate > mild), the most serious causality (related > not related), the most serious seriousness (Yes > No), the last action taken, and the last outcome will be chosen.

SAE, AEs leading to treatment discontinuation, AEs leading to study discontinuation and fatal AEs will be presented in listings. In these listings of AEs, the relative day counted from the day of the first administration of study treatment will be presented. Relative day will only be calculated if AE start date is complete.

12.4. Vital Signs

Vitals signs will be analysed by means of the appropriate descriptive statistics for:

- Absolute values at each time-point by treatment, from screening to EoS/ET.
- Absolute changes from baseline to each time-point by treatment.

- Shift tables of vital signs abnormalities by treatment. At each assessment time-point each vital sign will be classified as Normal, Abnormal Not Clinically Significant (NCS) and Abnormal Clinically Significant (CS).

Vital signs will also be presented in a by-patient listing.

Vital signs data will be presented for both the core study and Follow-up Period CCI [redacted]

12.5. Physical examination

Physical examination (Normal/Abnormal NCS/Abnormal CS) will be tabulated by treatment group, with numbers and percentages.

- Absolute values for weight and height (height only presented at screening).
- Frequency tables of body system abnormalities. Each body system at each assessment will be classified as Normal, Abnormal NCS and Abnormal CS.

Physical examination will also be presented in a by-patient listing.

Physical examination data will be presented for both the core study and Follow-up Period CCI [redacted]

12.6. Clinical Laboratory parameters

Laboratory assessments include standard hematology and blood chemistry.

The following will be presented using descriptive statistics in laboratory quantitative parameters:

- Absolute values at screening and at EoS/ET visit.
- Changes from screening to EoS/ET.
- Shift tables of laboratory values abnormalities by treatment. At each scheduled visit, each laboratory parameter will be classified as Normal, Abnormal NCS and Abnormal CS.

Laboratory assessments will also be presented in by-patient listings.

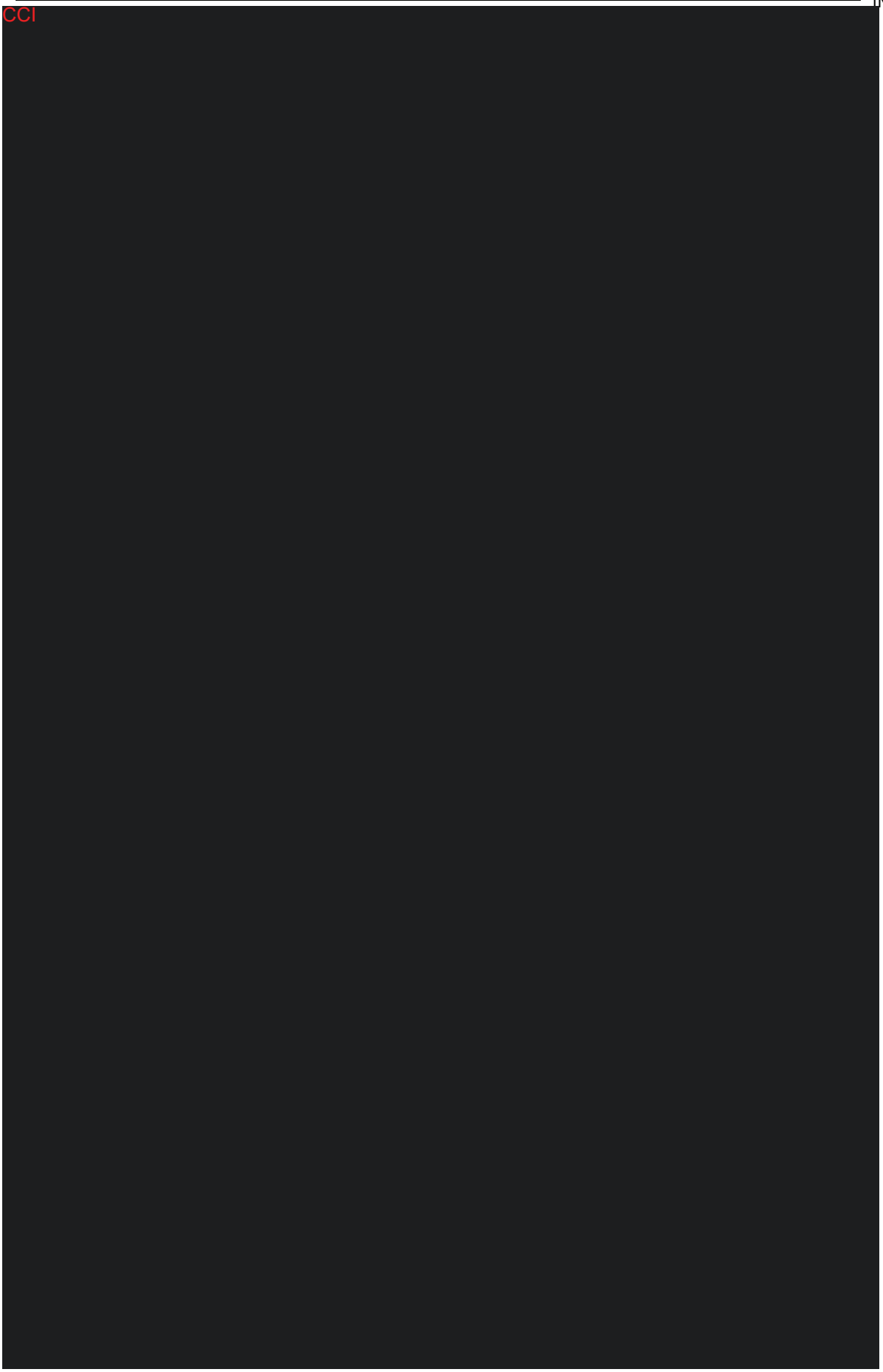
Clinical laboratory data will be presented for both the core study and Follow-up Period CCI [redacted]

12.7. Overall number of courses of tirbanibulin received

For the core study, the overall number of courses of tirbanibulin received per patient from baseline to Week 16 (1 or 2) will be summarised using SAF population. CCI [redacted]

CCI [redacted]

CCI



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[redacted]

15. Interim analyses

No interim analysis will be performed in this trial.

Nevertheless, it is important to note that the overall study has 2 periods during which treatment may be administered, the Treatment and Response Assessment Period (core study) and the Follow-Up Period, and consequently there will be 2 different result deliveries according to 2 different database locks. The first results delivery will be at the end of the core study, including efficacy and safety up to Day 113/ET (Week 16). The second results delivery will be after finalizing the Follow-Up Period at Week 48/ET and will include the overall safety results.

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[redacted]

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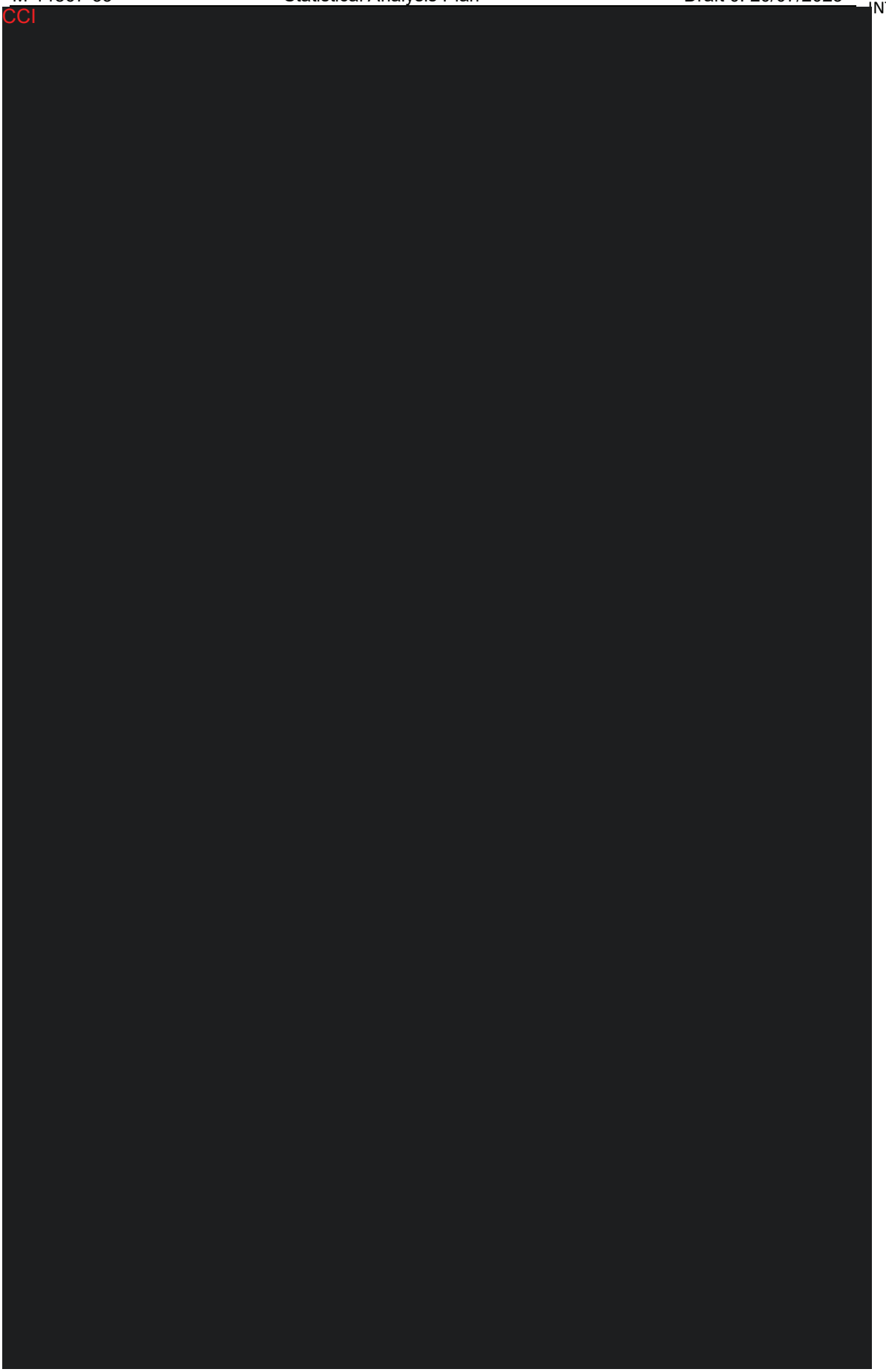

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16.4. Unscheduled and Repeated Tests

Unscheduled Tests

As deemed necessary by the Investigator, additional safety test(s) can be performed at any time during the trial in order to follow-up the progress of any clinically relevant abnormal finding, investigate any potential new adverse event, etc. These additional tests outside of the initial schedule of the trial will be considered “unscheduled tests” and will not be associated with any trial visit.
Unscheduled tests will not be comparable between patients, these tests will only be presented in the listings.

Repeated Tests

Any safety test may be repeated at the Investigator’s discretion under either of the following situations:

- When there is any kind of problem with the first test (i.e., blood sample haemolyzed, presence of artifacts, etc.). The Investigator should repeat the individual test as soon as possible.
- At the screening visit any individual test(s) may be reasonably repeated in respect of the eligibility criteria (e.g., laboratory sample when there is any clinically significant abnormality, etc.).

The new test will be considered a “re-test” and will be identified with the same visit identification as the first attempt.

For the analysis tables, the most updated test at each visit will be used. Nevertheless, all test results (first and re-test when available) will be presented on the listings.

CCI

[redacted]

18. References

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CCI

CCI

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Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Stat Med. 2009;28:586-604.

Bretz F, Maurer W, Hommel G. Test and power considerations for multiple endpoint analyses using sequentially rejective graphical procedures. Stat Med. 2011 Jun 15;30(13):1489-501.

Bretz F, Maurer W, Maca J. Graphical Approaches to Multiple Testing. In: Young WR, Chen D, editors. Clinical Trial Biostatistics and Biopharmaceutical Applications. New York: Chapman and Hall/CRC; 2014. p.350-393

CCI

Farrington CP. Quantifying misclassification bias in cohort studies of vaccine efficacy. Stat Med. 1990 Nov;9(11):1327-37.

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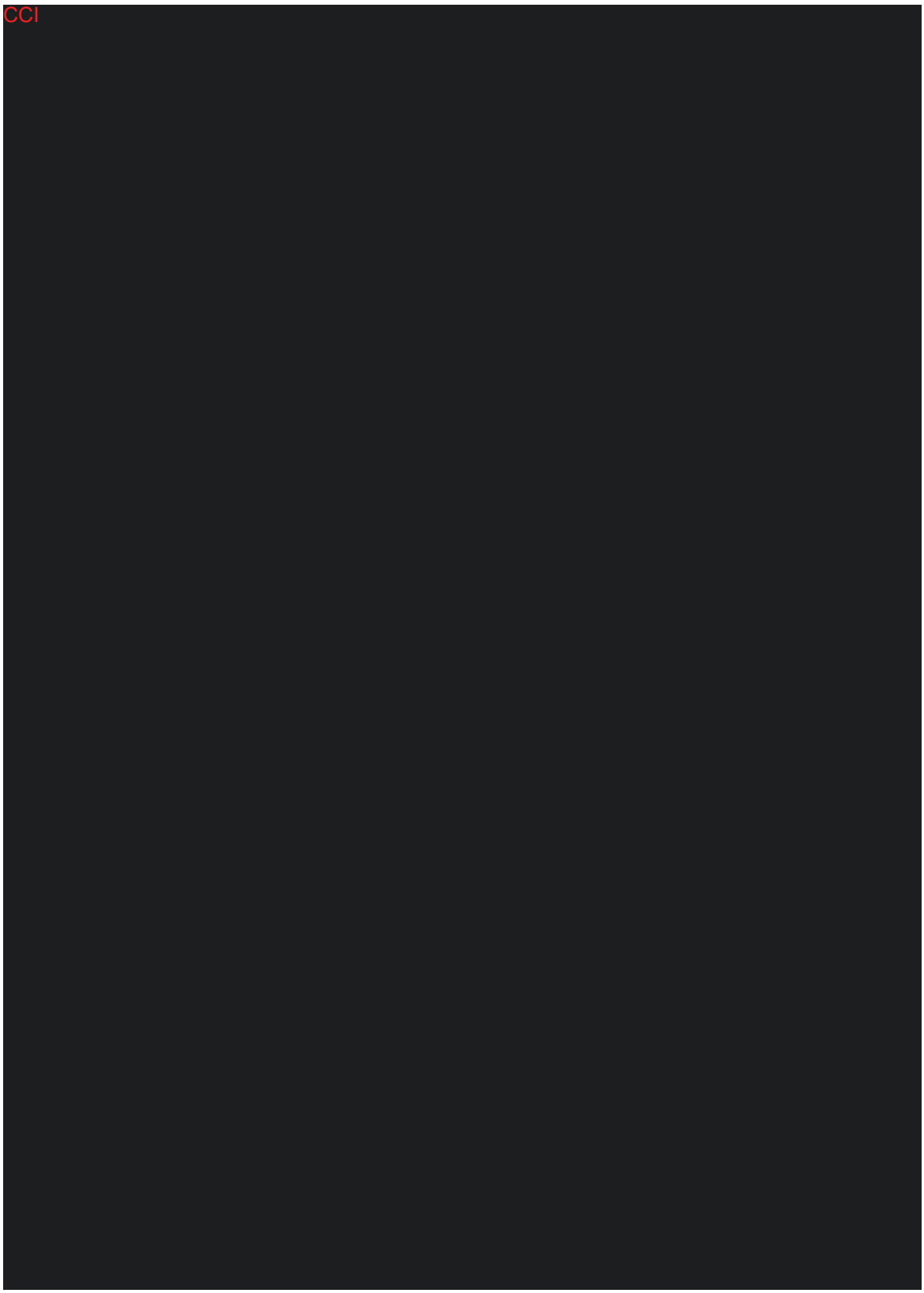
19. INDEX OF TABLES, GRAPHICS AND LISTINGS

The study name, the path and the name of the program used will be referred for each table and listing. Tables, graphs and listings will be enumerated following the International Conference on Harmonisation E3. All raw and all calculated data of all patients taking part in the trial will be presented in data listings. These listings will be sorted by treatment and patient. Any abbreviation will be explained in a footnote.

The index of tables, graphics and listings will be presented in separate document together with their respective shells.

20. SHELLS OF TABLES, GRAPHICS AND LISTINGS

The shells of tables, graphics and listings will be presented in separate document.



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