STATISTICAL ANALYSIS PLAN

ISONAM
- PMCF study -

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HISTORY OF VERSIONS

Version number	Date	Author	Changes compared to the previous version	
1.0	22/05/2023	C. GENTIL	C	
1.1	04/09/2023	C. GENTIL	M	For concomitant medications, use of Safety Set population instead of FAS population For Adverse Events, simplification of tables (related to nasal swab and related to CRS grouped as not related to study device) Add Data Review meeting date

A: Addition, C: Creation, D: Deletion, M: Modification

APPROVAL OF THE STATISTICAL ANALYSIS PLAN

Protocol	LPH-2102
Meeting of the Committee of Validation for the Data-Review	09/08/2023
Statistical Analysis Plan	04/09/2023

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LIST OF ABBREVIATIONS

16S rRNA	16S ribosomal RNA
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical Classification
CE	Conformité Européenne
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRO	Contract Research Organisation
CRS	Chronic RhinoSinusitis
Dx	Day x
[E]	Number of events
FAS	Full Analysis Set
ICH	International Conference on Harmonisation
MD	Medical Device
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
PMCF	Post Market Clinical Follow-Up
PP	Per Protocol
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
RNA	Ribo Nucleic Acid
SAS®	Statistical Analysis System
SAE	Serious Adverse Event
SNOT-22	Sino Nasal Outcome Test-22
SOC	System Organ Class
TC	Telephone Call
TEAE	Treatment-Emergent Adverse Event
V1	Visit 1
V2	Visit 2
WHO-DRUG	World Health Organization Drug Dictionary

TABLE OF CONTENTS

1. INTRODUCTION

This statistical analysis plan is based on clinical investigation plan (CIP) LPH-2102 – version dated on June 14th, 2021. It defines populations of analysis and the evaluation methods of the principal and secondary criteria.

2. STUDY OBJECTIVES

2.1. Primary objective

The primary objective is to characterize the change of sino-nasal microbial communities from adult Chronic RhinoSinusitis (CRS) subjects via 16S ribosomal RNA (16S rRNA) gene high throughput sequencing before and after 1-month treatment duration with Healsea® Chronic.

2.2. Secondary objectives

The secondary objectives are

- To assess the efficacy of Healsea® Chronic in improving health-related quality of life of CRS adult subjects.
- To assess the global satisfaction of subjects with the use of Healsea® Chronic for CRS.
- Safety: to assess systemic and local tolerance of Healsea® Chronic over the study period.

3. STUDY DESIGN

This is a non-randomized, exploratory, monocentric, open label single-arm interventional study on medical device (PMCF investigation for medical device (MD) CE marked and used in its intended purpose with invasive and/or burdensome procedure as per Medical Device Regulation (MDR) Art. 74(1))

Investigational plan description (see Figure 1):

- Visit 1 (V1) – (Day 1): Screening/Inclusion
- Telephone call 1 (TC1) – (Day 15±3)
- Visit 2 (V2) – (Day 30±5): end of treatment

The maximal study duration for each subject is 35 days.

Visit name	Screening/Inclusion	At home	Telephone call	At home	End of Treatment
Visit Number	V1		TC1		V2
Days/Weeks	D1	D1 – D15± 3	D15±3	D15± 3 – D30± 5	D30 ± 5
Screening and General Assessments					
Patient information and Consent collection	X				
Eligibility criteria	X				
Demography and Medical history	X				
Physical and clinical examination	X				X
Ongoing medication	X				
Treatment					
Healsea® Chronic		X		X	
Assessments					
SNOT 22	X				X
Collection of middle meatus swab specimens	X				X
Adverse Events/incidents and concomitant medication reporting	X		X		X
Satisfaction questionnaire					X
Compliance to study product					X

Figure 1 : Flow chart of the study

4. SAMPLE SIZE

An arbitrary sample of 20 subjects completing the investigation without major protocol deviation has been chosen.

5. DEFINITION OF THE ANALYSIS SETS

Screened subjects: all subjects who signed an informed consent

Included subjects: all screened subjects who will have been expected to participate in the study.

Safety Set: all subjects who will have used the investigational medical device at least once.

Full Analysis Set (FAS): all subjects from the Safety Set who will have at least one post baseline Sino Nasal Outcome Test-22 (SNOT-22) evaluation.

Per Protocol Set (PP): all subjects from the FAS without any major protocol deviation.

The status of protocol deviations (minor or major) will be validated during the data review meeting.

Any subject not satisfying major entry criteria or for whom post inclusion data are not available will be identified by the Validation Committee during the data review, and could be excluded from the FAS Set in agreement with circumstances exposed in the ICH-E9 §5.2.1.

Safety analysis will be performed on the Safety Set.
Efficacy analysis (except primary efficacy criterion) will be performed on the FAS.

Note: primary efficacy criterion (16S rRNA gene high throughput sequencing) will be analysed separately by a dedicated team specialized in microbiome analysis.

6. STATISTICAL METHODS

6.1. Data processing

The analyses will be computed with SAS Version 9.4 TS Level 1M6 Copyright (c) 2016 by SAS Institute Inc., Cary, NC, USA.

6.2. Description

The number of available data and/or the number of missing data will be given and the following descriptive statistics will be provided:

- For quantitative parameters: mean, standard deviation (SD), median, Q1, Q3, extreme values (min and max).

  In this case, calculated statistics (mean, standard deviation, median, Q1, Q3) will generally be displayed with one more significant figure than the observed data, unless the described variable necessitates less precision.

- For qualitative parameters: number and percentage of each modality.

  Usually, one decimal digit will be given. A second decimal digit could be provided to improve the display, if required.

6.3. Statistical/Analytical issues

6.3.1. Significance level

All statistical analyses will be performed at the 0.05 global significance level (type I error rate), using two-sided tests.

Because of the exploratory nature of the study, all the statistical results have to be considered within a descriptive perspective and not as inferential issues. No adjustment for Type I error is done. P-values of statistical tests will be provided for information only.

6.3.2. Interim analysis

No interim analysis will be performed.

6.3.3. Handling of dropouts and missing data

a) Repositioning of visits

Not applicable.

b) Partially filled scales (if applicable)

The SNOT-22 questionnaire can be analysed when there are missing data, if less than 50% of items are missing. A higher proportion of missing items makes the questionnaire unsuitable for statistical analysis.
For the SNOT-22 questionnaire with missing data, provided more than 50% of items have been completed, a total score will be imputed from the completed items (Hopkins, Gillett, Slack,

Lund, & Browne, 2009) by use of a mean individual technique (Roth, Switzer, & Switzer, 1999): for a given subject, if an item is missing, its value will be imputed by the mean of the non-missing items of SNOT-22 for the same subject.

c) Missing data (other than dropouts)

Missing data will not be estimated and will be treated as missing data for the statistical analysis.

Concerning missing dates, see §6.4

d) Dropouts

Subjects from Safety Set who prematurely discontinued the study will be included in the analysis.

No method will be applied to replace missing data.

6.4. General conventions and/or calculated variables

6.4.1. Subject reference start/end dates

For each subject, the reference dates will be the following:

- The reference start date is the date of inclusion visit.
- The reference end date is the date when subject was determined to have ended the trial.

6.4.2. Computation of a duration

The formulae below will be generally used:

- Duration (in days) = Date#2 – Date#1 + 1 day

6.4.3. Missing dates of inclusion visit or end of study

Missing dates of the inclusion visit will be considered equal to the inclusion date.
Missing dates of end of study will be reviewed by the members of the Validation Committee and extrapolated using all information recorded.

6.4.4. Missing start/end dates of adverse events / incidents / expected side effects

In the following paragraphs, adverse events, incidents and expected side effects will be referred to as "adverse events" for ease of reading.

a) Start date

Completely missing date: it will be estimated by the reference start date.

If the day and the month are missing:

- If the year = year of reference start date, it will be estimated by the reference start date
- If the year < year of reference start date, it will be estimated by the 31st December

- If the year > year of reference start date, it will be estimated by the 1st January

If only the day is missing:
- If the month/year = month/year of reference start date, it will be estimated by the date of reference start date
- If the month/year < month/year of reference start date, it will be estimated by the last day of the month
- If the month/year > month/year of reference start date, it will be estimated by the first day of the month

If after imputation, the estimated start date is after the end date of the adverse event, it will be replaced by the end date of the adverse event.

b) End date

Note: the following rules concern events that are not "ongoing" at the end of the study.

Completely missing date: it will be estimated by the reference end date

If the day and the month are missing:
- If the year = year of reference end date, it will be estimated by the reference end date
- If the year < year of reference end date, it will be estimated by the 31st December
- If the year > year of reference end date, it will be estimated by the 1st January

If only the day is missing:
- If the month/year = month/year of reference end date, the it will be estimated by the reference end date
- If the month/year < month/year of reference end date, the it will be estimated by the last day of the month
- If the month/year > month/year of reference end date, the it will be estimated by the first day of the month

If after imputation, the estimated end date is before the start date of the adverse event, it will be replaced by the start date of the adverse event.

6.4.5. Missing start/end dates of concomitant medications

Same rules as for adverse events.

7. STUDY SUBJECTS

7.1. Disposition of subjects

Screened subjects (signed informed consent) and included subjects will be summarised using frequencies and percentages as well as reasons of non-selection/non-inclusion, if applicable.
The number and percentage of subjects who withdrew prematurely after inclusion, are lost to follow-up as well as the number of completers will be described.
All withdrawn subjects after their inclusion will be described regarding their main reason for withdrawal.

7.2. Protocol deviations

Protocol deviations will be discussed during the data review meeting and the status (minor or major) of these deviations will be validated in order to identify the subjects to be excluded from the PP set.

Major deviations are identified by:
- Non-compliance with the inclusion and exclusion criteria;
- Non-compliance with treatment;
- No collection of middle meatus swab sample at any visit;
- Intake of forbidden medication, i.e. nasal irrigation.

All other deviations will a priori be considered as minor.

All major and minor deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment will be listed by subjects.

7.3. Data Sets Analysed

The number and percentage of subjects in each analysis data set, as described in §5, will be provided.

8. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Baseline safety characteristics will be described on the Safety Set.
All demographic and baseline characteristics (including safety characteristics) will be described on the FAS.

8.1. Demographic characteristics

Age (years) and sex will be summarised using descriptive statistics already mentioned.

Age (years) = (reference start date – date of birth) / 365.25 *(rounded at 1 digit)*

8.2. Previous and concomitant medications

Previous and concomitant medications (taken at least once before reference start date) are coded by ATC class and substance name using the WHO-DRUG dictionary version 2022 Q1.

They will be summarised with frequencies and percentages.

Subjects will be counted only once within these ATC categories.

8.3. Medical and surgical past history

Medical and surgical past history is coded using the MedDRA dictionary version 25.0. Diseases are classified by System Organ Class (SOC) and Preferred Term (PT).

The number and percentage of subjects with at least one disease of each category (SOC/PT) will be given.

Subjects will be counted only once within these categories.

8.4. Baseline efficacy variables

Each item of the SNOT-22 and the resulting score will be described at baseline.
The following sub-domains of the SNOT-22 will be described:

- Nasal domain based on items 1-2-3-4-5-6-21-22
- Ear/facial domain based on items 7-8-9-10
- Sleep domain based on items 11-12-13-14
- Function domain based on items 15-16-17
- Emotion domain based on items 18-19-20

8.5. Baseline safety variables

Adverse events since enrolment will be described at baseline.
Serious adverse events potentially related to the sino-nasal swab procedure will be described at baseline.

8.6. Other baseline variables

Sino-nasal symptoms will be described at baseline.
Rhinologic examination will be described at baseline.

9. COMPLIANCE

Compliance will be calculated according to the following formula and analysed on the Safety Set:

Compliance (%) = Real quantity used (g)*100/ Theoretical quantity used (g)

With:

- Initial weight = 199.5 g
- Theoretical weight after 30 days of treatment (g) = 154.5 g
- Theoretical quantity used (g) = 199.5 – 154 = 45 g
- Real quantity used (g) = 199.5 - Final weight (g)

In case of trial spray not returned, compliance will be considered unknown and missing.

Note:

- The analysis of compliance will be purely descriptive.
- Usually, only the global compliance will be estimated.

10. EFFICACY

Subjects will be analysed on the FAS for all items collected in the case report form (CRF.)

Secondary efficacy criteria will be described at each assessment time, as well as changes from baseline (when applicable), in accordance with the chapter §6.2.

10.1. Analysis of the primary efficacy criterion

Analysis of primary efficacy criterion (16S rRNA gene high throughput sequencing) will be described in a separate document. The analysis population will be defined according to the results of the sequencing process.

10.2. Analysis of the secondary efficacy criteria

Each item of the SNOT-22, the nasal, ear/facial, sleep, function and emotion sub-domains (refer to §8.4 for definition) and the resulting overall score and change from baseline will be described at end of study.

Subject satisfaction (questions on 4-point Likert scale) will be described at end of study.
Symptoms of chronic rhino sinusitis and change from baseline will be described at end of study.

11. SAFETY

The following parameters will be analysed on the Safety Set.

11.1. Study duration

Study duration will be calculated according to the formulas below:

Study duration (days) = Reference End Date – Reference Start Date + 1

11.2. Adverse events

Note: in the following paragraph, for a smoother reading:

- Incidents and adverse events will be referred as adverse events (AE);
- treatment-emergent incidents and adverse events will be referred as treatment-emergent adverse event (TEAE).

AE are coded using the MedDRA dictionary version 25.0. They are classified by System Organ Class and Preferred Term.

An AE will be considered as a TEAE if:

- it was no present prior to the reference start date
- it was present prior to the reference start date and worsened during the study (increase of intensity)
- it reappears after the reference start date (finished before the reference end date)

A given TEAE (according to the MedDRA terminology) will be counted only once per subject. If a subject experienced several AEs in the same SOC/PT, the most severe intensity will be retained for this SOC/PT.
Note: if the intensity/severity is missing, a conservative approach will be adopted and the intensity/severity will be considered as severe.

Missing or incomplete dates will be estimated as described in section §6.4.4 in order to determine the TEAEs, but they will be presented as reported in CRF in the data listings. Generally, an AE for which the onset date is missing or incomplete and does not permit to identify the onset according to the date of the reference start date (i.e. missing onset day and month/year corresponding to the reference start date) will be considered as treatment-emergent.

Tables will present separately:

- **incidents related to the use of the medical device** (described as possibly related, probably related or related with the device in the eCRF),
- **adverse events not related to the use of the medical device**

- Summary of adverse-events

Summary tables will be produced for AEs not related to the use of medical device and for incidents related to the use of the medical device. Tables will be adapted depending on the definition of the type of AE

- number and percentage of subjects with at least one adverse event (AE)
- number and percentage of subjects with at least one AE leading to definitive study device discontinuation
- number and percentage of subjects with at least one AE leading to definitive study discontinuation
- number and percentage of subjects with at least one serious adverse event (SAE)
- number and percentage of subjects with at least one TEAE
    - number and percentage of subjects with one TEAE
    - number and percentage of subjects with two TEAE
    - number and percentage of subjects with at least three TEAE

- Analysis of treatment-emergent adverse event

Only TEAE will be summarised by System Organ Class and Preferred term. The following tables will be provided:

- number and percentage of subjects with TEAE for AEs related to the chronic rhino sinusitis,
- number and percentage of subjects with TEAE for AEs related to the sino-nasal swab procedure,
- number and percentage of subjects with TEAE for incidents related to the use of the medical device

- Analysis of deaths, other serious adverse events and other significant adverse events

A listing of deaths will be provided if applicable.

A listing of serious adverse events will be also provided if applicable.

All AEs leading to definitive discontinuation of the trial device or definitive discontinuation of the trial will be listed if applicable.

11.3. Concomitant treatments

Concomitant treatments are coded using the WHO-DRUG dictionary version 2022 Q1.

All treatments taken at least once after reference first date or appeared during the study will be summarised by Anatomical Therapeutic Class (ATC) and substance name. The number and percentage of subjects in each category will be computed.

Subjects will be counted only once within these ATC categories.

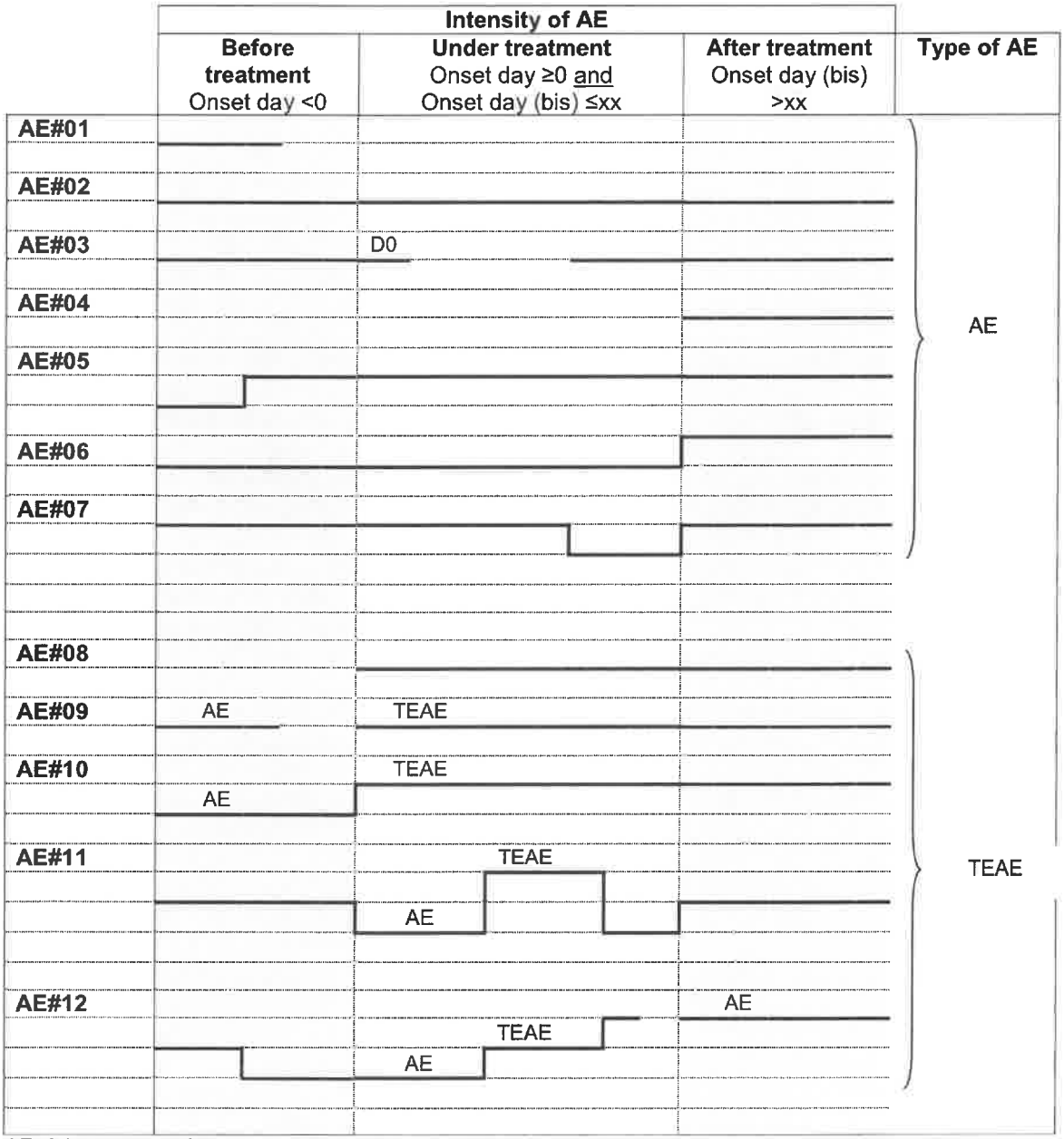
Note: a medication which began before the reference start date and is on-going after the reference start date is counted in "previous medications" (see §8.2) and in "concomitant medications".

12. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

After data review, considering no serious adverse event related to the nasal swab occurred, display of AE is split between 2 categories "incident related to the study device" and "AE not related to the study device" instead of the former 3 categories (incident, AE related to nasal swab procedure and AE related to chronic rhinosinusitis).

13. APPENDICES

13.1. Treatment emergent adverse events



AE: Adverse event / TEAE: Treatment emergent adverse event
Onset day = AE start date – Date of reference start date
Onset day (bis) = AE start date – Date of reference end date
D0 ➔ Onset day = 0

Figure 2 : Treatment emergent adverse events

13.2. List of statistical tables, figures and listings

Type	Number	Title
STUDY SUBJECTS		
Table	14.1.1.1	Subjects disposition [Screened subjects]
Figure	14.1.1.1	Subjects disposition [Screened subjects]
Listing	14.1.1.1	Not included / excluded subjects – Reasons [Screened subjects]
Table	14.1.1.2	Summary of protocol deviations [Included subjects]
Listing	14.1.1.2	Subjects with at least one major protocol deviation [Included subjects]
Table	14.1.1.3	Premature withdrawal – Reason of withdrawal [Included subjects]
Listing	14.1.1.3	Subjects prematurely withdrawn [Included subjects]
DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS		
Table	14.1.2.1	Baseline – Demographic Characteristics [FAS]
Table	14.1.2.2	Baseline – Medical and surgical past history [FAS]
Listing	14.1.2.2	Baseline – Subjects with a medical or surgical history [FAS]
Table	14.1.2.3	Baseline – Number (%) of subjects with at least one previous or concomitant medication, by WHO-Drug ATC class and substance name [FAS]
Table	14.1.2.4	Baseline - SNOT-22 Symptoms of chronic rhinosinusitis scores [FAS]
Table	14.1.2.5.1	Baseline – Baseline safety variables – Adverse events since enrolment [FAS]
Table	14.1.2.5.2	Baseline – Baseline safety variables – Serious Adverse events potentially related to the sino-nasal swab procedure [FAS]
Table	14.1.2.6	Baseline – Other baseline variables [FAS]
EFFICACY		
Table	14.2.1	Secondary efficacy criteria – SNOT-22 score [FAS]
Table	14.2.2	Secondary efficacy criteria – Subject satisfaction [FAS]
Table	14.2.3	Secondary efficacy criteria – Symptoms of chronic rhino sinusitis [FAS]
Table	14.2.4	Secondary efficacy criteria – Weight of device [FAS]
SAFETY		
Table	14.3.1.1	Safety – Study duration by subject [Safety Set]
Table	14.3.1.2	Safety – Summary of compliance [Safety Set]
Table	14.3.1.3	Safety – Concomitant treatments [Safety Set]
SAFETY – Adverse events		

Type	Number	Title
Table	14.3.2.1	Safety – Brief summary of incidents related to the use of the medical device [Safety Set]
Table	14.3.2.2	Safety – Brief summary of adverse events not related to the use of the medical device [Safety Set]
Table	14.3.2.3	Safety – TEAE (incidents) related to the use of the medical device by System Organ Class and preferred term [Safety Set]
Table	14.3.2.4	Safety – TEAE not related to the use of the medical device by System Organ Class and preferred term [Safety Set]
Table	14.3.2.5	Safety – Serious TEAE (incidents) related to the use of the medical device by System Organ Class and preferred term [Safety Set]
Table	14.3.2.6	Safety – Serious TEAE not related to the use of the medical device by System Organ Class and preferred term [Safety Set]
SUBJECTS DATA LISTINGS		
Listing	16.2.1	Discontinued subjects
Listing	16.2.2	Protocol deviations
Listing	16.2.3	Subjects excluded from the efficacy analysis
Listing	16.2.4	Demographic data
Listing	16.2.5	Compliance data
Listing	16.2.6	Individual efficacy response data

13.3. Mock tables

Table 14.1.1.1. Subjects disposition [Screened subjects]

	Healsea Chronic N=XX
Analysis Sets	
Screened subjects	XX (100.0%)
Included subjects	XX (XX.X%)
Safety Set	XX (XX.X%)
Full Analysis Set	XX (XX.X%)
Per Protocol Set	XX (XX.X%)

Figure 14.1.1.1. Subjects disposition [Screened subjects]

Listing 14.1.1.1. Not included / excluded subjects – Reasons [Screened subjects]

ID – Sex – Age	Category	Inclusion / Exclusion criterion	Answer
	Inclusion Exclusion		No Yes

Table 14.1.1.2 Summary of protocol deviations [Included subjects]

	Healsea Chronic N=XX
Subjects with at least one protocol deviation	
All	XX (XX.X%)
Category of deviation	
Minor	XX (XX.X%)
Major	XX (XX.X%)

Listing 14.1.1.2 Subjects with at least one major protocol deviation [Included subjects]

ID – Sex – Age	Treatment	Safety Set	Full Analysis Set	Per-Protocol Set	Protocol deviation	Classification of deviation
	Healsea Chronic Healsea Chronic					

Table 14.1.1.3. Premature withdrawal – Reason of withdrawal [Included subjects]

	Healsea Chronic N=XX
Reason of premature withdrawal	
XXXXXXX	XX (XX.X%)

Listing 14.1.1.3 Subjects prematurely withdrawn [Included subjects]

ID – Sex – Age	Treatment	Safety Set	Full Analysis Set	Per-Protocol Set	Reason of withdrawal
	Healsea Chronic Healsea Chronic				

Table 14.1.2.1. Baseline - Demographic characteristics [FAS]

	Healsea Chronic N=XX
Age (years)	
N	XX
Missing	XX
Mean (SD)	XX.X (XX.X)
Median	XX
Q1/Q3	XX / XX
Min/Max	XX / XX
Sex	
N	XX
Missing	XX
Female	XX (XX.X%)
Male	XX (XX.X%)

Table 14.1.2.2. Baseline - Medical and surgical past history [FAS]

SOC - Preferred Term	Healsea Chronic N=XX
Subjects with at least one medical history	
All	XX (XX.X%)
XXXXX	
All	XX (XX.X%)
XXXXX	XX (XX.X%)
XXXXX	XX (XX.X%)

Listing 14.1.2.2 Baseline – Subjects with a medical or surgical history [FAS]

ID – Sex – Age	Treatment	Safety Set	Full Analysis Set	SOC	Preferred term	Start date / end date
	Healsea Chronic					
	Healsea Chronic					

Table 14.1.2.3. Baseline – Number (%) of subjects with at least one previous or concomitant medication, by WHO-Drug ATC class and substance name [FAS]

ATC1 - ATC2	Healsea Chronic N=XX
Subjects with at least one previous medication	
All	XX (XX.X%)
XXXXX	
All	XX (XX.X%)
XXXXX	XX (XX.X%)
XXXXX	XX (XX.X%)

Table 14.1.2.4. Baseline - SNOT-22 Symptoms of chronic rhinosinusitis scores [FAS]

	Healsea Chronic N=XX
XXXXX score	
N	XX
Missing	XX
Mean (SD)	XX.X (XX.X)
Median	XX
Q1/Q3	XX / XX
Min/Max	XX / XX
Total score	
N	XX
Missing	XX
Mean (SD)	XX.X (XX.X)
Median	XX
Q1/Q3	XX / XX
Min/Max	XX / XX

Table 14.1.2.5.1. Baseline – Baseline safety variables – Adverse events since enrolment [FAS]

	Healsea Chronic N=XX	
	n (%)	[E]
Number and percentage of subjects with / Number of		
Incident	XX (XX.X%)	XXX
Incident leading to definitive study device discontinuation	XX (XX.X%)	XXX
Serious incident	XX (XX.X%)	XXX

Table 14.1.2.5.2. Baseline – Baseline safety variables – Serious Adverse events potentially related to the sino-nasal swab procedure [FAS]

	Healsea Chronic N=XX	
SOC - Preferred Term	n (%)	[E]
Serious Adverse events potentially related to the sino-nasal swab procedure		
All	XX (XX.X%)	XXX
XXXXX		
All	XX (XX.X%)	XXX
XXXXX	XX (XX.X%)	XXX
XXXXX	XX (XX.X%)	XXX

Table 14.1.2.6. Baseline – Other baseline variables [FAS]

	Healsea Chronic N=XX
XXXX sino-nasal symptom	
N	XX
Missing	XX
Yes	XX (XX.X%)
No	XX (XX.X%)
N	XX
Missing	XX
Lasting for 12 weeks or longer	XX (XX.X%)
For less than 12 weeks	XX (XX.X%)
XXXX rhinologic examination	
N	XX
Missing	XX
Yes	XX (XX.X%)
No	XX (XX.X%)

Table 14.2.1. Secondary efficacy criteria - SNOT-22 score [FAS]

	Healsea Chronic N=XX
XXXXX score – End of Study	
N	XX
Missing	XX
Mean (SD)	XX.X (XX.X)
Median	XX
Q1/Q3	XX / XX
Min/Max	XX / XX
XXXXX score – Change from baseline	
N	XX
Missing	XX
Mean (SD)	XX.X (XX.X)
Median	XX
Q1/Q3	XX / XX
Min/Max	XX / XX
Total score – End of Study	
N	XX
Missing	XX
Mean (SD)	XX.X (XX.X)
Median	XX
Q1/Q3	XX / XX
Min/Max	XX / XX
Total score – Change from baseline	
N	XX
Missing	XX
Mean (SD)	XX.X (XX.X)
Median	XX
Q1/Q3	XX / XX
Min/Max	XX / XX

Table 14.2.2. Secondary efficacy criteria – Subjects satisfaction [FAS]

	Healsea Chronic N=XX
How would you characterize the use of Healsea Chronic nasal spray?	
N	XX
Missing	XX
0: not easy	XX (XX.X%)
1: pretty easy	XX (XX.X%)
2: easy	XX (XX.X%)
3: very easy	XX (XX.X%)
How would you characterize the residual taste after spraying Healsea Chronic?	
N	XX
Missing	XX
0: not pleasant	XX (XX.X%)
1: neutral	XX (XX.X%)
2: pleasant	XX (XX.X%)
3: very pleasant	XX (XX.X%)
How would you characterize the cleansing and moistening of nasal mucosa with Healsea Chronic?	
N	XX
Missing	XX
0: no improvement	XX (XX.X%)
1: slight improvement	XX (XX.X%)
2: moderate improvement	XX (XX.X%)
3: very clear improvement	XX (XX.X%)

Table 14.2.3. Secondary efficacy criteria – Symptoms of chronic rhinosinusitis [FAS]

	Healsea Chronic N=XX
XXXX sino-nasal symptom – End of study	
N	XX
Missing	XX
Yes	XX (XX.X%)
No	XX (XX.X%)
XXXX sino-nasal symptom – Change from baseline	
N	XX
Missing	XX
Improvement	XX (XX.X%)
No change – symptom present	XX (XX.X%)
No change – symptom absent	XX (XX.X%)
Degradation	XX (XX.X%)

Table 14.2.4. Safety - Secondary efficacy criteria – Weight of device [FAS]

	Healsea Chronic N=XX
Returned device	
N	XX
Missing	XX
Yes	XX (XX.X%)
No	XX (XX.X%)
Weight of returned device	
N	XX
Missing	XX
Mean (SD)	XX.X (XX.X)
Median	XX
Q1/Q3	XX / XX
Min/Max	XX / XX

Table 14.3.1.1. Safety - Study duration by subject [Safety Set]

	Healsea Chronic N=XX
Study duration (days)	
N	XX
Missing	XX
Mean (SD)	XX.X (XX.X)
Median	XX
Q1/Q3	XX / XX
Min/Max	XX / XX

Table 14.3.1.2. Safety - Summary of compliance [Safety Set]

	Healsea Chronic N=XX
Compliance (%)	
N	XX
Missing	XX
Mean (SD)	XX.X (XX.X)
Median	XX
Q1/Q3	XX / XX
Min/Max	XX / XX

Table 14.3.1.3. Safety – Concomitant treatments [Safety Set]

ATC1 - ATC2	Healsea Chronic N=XX
Subjects with at least one concomitant treatment	
All	XX (XX.X%)
XXXXX	
All	XX (XX.X%)
XXXXX	XX (XX.X%)
XXXXX	XX (XX.X%)

Table 14.3.2.1 Safety – Brief summary of incidents related to the use of the medical device [Safety Set]

	Healsea Chronic N=XX	
	n (%)	[E]
Number and percentage of subjects with related / Number of related		
Incident	XX (XX.X%)	XXX
Incident leading to definitive study device discontinuation	XX (XX.X%)	XXX
Incident leading to definitive study discontinuation	XX (XX.X%)	XXX
Serious incident	XX (XX.X%)	XXX
At least one treatment-emergent incident	XX (XX.X%)	XXX
Exactly one treatment-emergent incident	XX (XX.X%)	XXX
Exactly two treatment-emergent incident	XX (XX.X%)	XXX
At least three treatment-emergent incidents	XX (XX.X%)	XXX

Table 14.3.2.2 Safety – Brief summary of adverse events not related to the use of the medical device [Safety Set]

	Healsea Chronic N=XX	
	n (%)	[E]
Number and percentage of subjects with related / Number of related		
Incident	XX (XX.X%)	XXX
Incident leading to definitive study device discontinuation	XX (XX.X%)	XXX
Incident leading to definitive study discontinuation	XX (XX.X%)	XXX
Serious incident	XX (XX.X%)	XXX
At least one treatment-emergent incident	XX (XX.X%)	XXX
Exactly one treatment-emergent incident	XX (XX.X%)	XXX
Exactly two treatment-emergent incident	XX (XX.X%)	XXX
At least three treatment-emergent incidents	XX (XX.X%)	XXX

Table 14.3.2.3. Safety – TEAE (incidents) related to the use of the medical device by System Organ Class and preferred term [Safety Set]

	Healsea Chronic N=XX	
SOC - Preferred Term	n (%)	[E]
Related treatment-emergent adverse events		
All	XX (XX.X%)	XXX
XXXXX		
All	XX (XX.X%)	XXX
XXXXX	XX (XX.X%)	XXX
XXXXX	XX (XX.X%)	XXX

Table 14.3.2.4. Safety – TEAE not related to the use of the medical device by System Organ Class and preferred term [Safety Set]

	Healsea Chronic N=XX	
SOC - Preferred Term	n (%)	[E]
Related treatment-emergent adverse events		
All	XX (XX.X%)	XXX
XXXXX		
All	XX (XX.X%)	XXX
XXXXX	XX (XX.X%)	XXX
XXXXX	XX (XX.X%)	XXX

Table 14.3.2.5. Safety – Serious TEAE (incidents) related to the use of the medical device by System Organ Class and preferred term [Safety Set]

SOC - Preferred Term	Healsea Chronic N=XX n (%)	[E]
Related treatment-emergent adverse events		
All	XX (XX.X%)	XXX
XXXXX		
All	XX (XX.X%)	XXX
XXXXX	XX (XX.X%)	XXX
XXXXX	XX (XX.X%)	XXX

Table 14.3.2.6. Safety – Serious TEAE not related to the use of the medical device by System Organ Class and preferred term [Safety Set]

SOC - Preferred Term	Healsea Chronic N=XX n (%)	[E]
Related treatment-emergent adverse events		
All	XX (XX.X%)	XXX
XXXXX		
All	XX (XX.X%)	XXX
XXXXX	XX (XX.X%)	XXX
XXXXX	XX (XX.X%)	XXX

14. BIBLIOGRAPHY

Hopkins, C., Gillett, S., Slack, R., Lund, V. J., & Browne, J. P. (2009, September). Psychometric validity of the 22-item Sinonasal Outcome Test. *Clinical Otolaryngology, 34*(5), pp. 447-454. doi:https://doi.org/10.1111/j.1749-4486.2009.01995.x

Roth, P. L., Switzer, F. S., & Switzer, D. M. (1999, July 1). Missing Data in Multiple Item Scales: A Monte Carlo Analysis of Missing Data Techniques. *Organizational Research Methods, 2*(3), pp. 211-232. doi:https://doi.org/10.1177/109442819923001