STATISTICAL ANALYSIS PLAN

TEACHER
- PMCF study -

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HISTORY OF VERSIONS

Version number	Date	Author	Changes compared to the previous version	
01	20/03/2023	K. CHAPDELAINE	C	

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

APPROVAL OF THE STATISTICAL ANALYSIS PLAN

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Statistical Analysis Plan	20/03/2023

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LIST OF ABBREVIATIONS

AE:	Adverse Event
ATC:	Anatomical Therapeutic Chemical Classification
AUC:	Area Under the Curve
CI:	Confidence Interval
COVID-19:	Coronavirus Disease 2019
CRF:	Case Report Form
CRO:	Contract Research Organisation
Dx:	Day x
[E]:	Number of events
FAS:	Full Analysis Set
ICH:	International Conference on Harmonisation
LOCF:	Last Observation Carried Forward
MedDRA:	Medical Dictionary for Regulatory Activities
NSAID:	Non-Steroidal Anti-Inflammatory Drugs
PMCF:	Post-Market Clinical Follow-up
PP:	Per Protocol
PT:	Preferred Term
Q1 / Q3:	First / Third Quartile
SAS®:	Statistical Analysis System
SD:	Standard deviation
SOC:	System Organ Class
TEAE:	Treatment-Emergent Adverse Event
Vy:	Visit y
WHO-DRUG:	World Health Organization Drug Dictionary
WURSS-21:	Wisconsin Upper Respiratory Symptom Survey – Short version

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1. INTRODUCTION

This statistical analysis plan is based on protocol LPH-2201 – version 1, dated on October 3rd, 2022. 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 compare the efficacy of Healsea® Rescue* and Placebo to improve the Quality of Life through symptoms of acute infectious rhinitis reduction in adults during a 7-day treatment period.

2.2. Secondary objectives

The secondary objectives are:

- To compare the efficacy of Healsea® Rescue* and of the Placebo to reduce the duration of each infectious rhinitis symptoms rated by the short version of the Wisconsin Upper Respiratory Symptom Survey (WURSS-21);
- To compare the efficacy of Healsea® Rescue* and of the Placebo to reduce the use of concomitant medication (antipyretics, systemic or local mucolytics, decongestants, antitussives, antibiotics);
- To compare the subject overall assessment on efficacy of Healsea® Rescue* and of the Placebo;
- Safety: to assess systemic and local tolerance of Healsea® Rescue* over the study period.

3. STUDY DESIGN

This is a prospective, interventional, double-blinded, placebo controlled, randomized, national (Bulgaria), monocentric PMCF study.

Investigational plan description (see Figure 1):

- **Visit 1 (V1) - (Day 1): Screening/Inclusion/Randomization**

Information and consent, demographic data and medical history, ongoing medication, physical and clinical examination (including COVID-19 antigen test), inclusion/non-inclusion criteria, randomization, e-diary presentation (including the first study questionnaire completion), reporting of adverse events, dispensation of Healsea® Rescue* Nasal Spray or Placebo (Isotonic nasal spray) (according to randomization list).

- **Day 1 (D1) - Day 8 (D8) (at home):**

Daily completion of the electronic diary (questionnaire, adverse events/incidents and concomitant medications), Healsea® Rescue* /Placebo nasal spray treatment daily administration.

- **D8 (Telephone call):**

End of Healsea® Rescue*/Placebo nasal spray treatment.

- **Day 9 (D9) - Day 13 (D13)/Day 15 (D15) (at home):**

Daily completion of the electronic diary (adverse events/incidents, concomitant medications, WURSS-21 if applicable, until the subject feels not sick for two consecutive days).

- **Visit 2 (V2) (D13/D15): end of study**

Physical and clinical examination (including COVID-19 antigen test), diary review, reporting of adverse events and incidents, compliance, subject satisfaction, WURSS-21 completion if the patient has not ticked "not sick" for 2 consecutive days in the previous days.

The maximal study duration for each patient is 15 days.

	Acute phase		Telephone call	Follow-up	
Visit name	Screening/Inclusion	At home		At home	End of study
Visit Number	**V1**		***TC1***		**V2**
Days/Weeks	D1	D1-D8	D8	D9-End of study visit	D13-D15
Informed consent	X				
Eligibility criteria	X				
Demography and Medical history	X				
Physical and clinical examination	X				X
COVID-19 antigen test	X				X
Ongoing medication	X				
Randomization	X				
Treatment (**Healsea® Rescue*** or Placebo) (14 intakes)		X			
Telephone call (End of **Healsea® Rescue*** or Placebo)			X		
Subject e-diary and WURSS 21	X*	X		X[$]	X*
(Serious) Adverse Events/ (serious) incidents and concomitant medication reporting	X	X		X	X
Satisfaction Questionnaire					X
Compliance					X

[$] After D8, WURSS-21 until complete resolution of symptoms for 2 consecutive days.

*WURSS-21 to be completed with the investigator on site at screening and at the end of the study if the patient still has not ticked "not sick" for 2 consecutive days in the previous days.

Figure 1 : Flow chart of the study

4. SAMPLE SIZE

A sample of 180 subjects (90 subjects per group) will be needed to provide 80% power with a one-sided test at a 0.05 significance level to detect a difference between Healsea® Rescue* and Placebo groups AUC of 30%.
Assuming that approximately 10% of subjects may drop-out the study, 200 subjects will be randomly assigned at a ratio 1:1 to Healsea® Rescue* and Placebo (100 subjects per group).

5. DEFINITION OF THE ANALYSIS SETS

Screened patients: all patients who signed an informed consent.

Included subjects: all screened subjects who participated in the study.

Randomised patients: all patients who signed an informed consent and who were assigned a treatment number.

Safety Set: all the randomised patients who took at least one puff of the nasal spray.

Full Analysis Set (FAS): all the randomised patients who took at least one puff of the nasal spray and with at least one post-baseline efficacy data.

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

Per-Protocol (PP) Set: Efficacy population based on the FAS without patients with major protocol deviations.

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

Safety endpoint will be performed on the Safety Set.

The analyses of primary and secondary endpoints will be performed on the FAS.
The primary endpoint will also be analysed on the PP set, analyses on the PP set being supportive in superiority trials. It will also be the case for one secondary endpoint (analysis of the AUC of the items 2 to 11 and 12 to 20 of the WURSS-21 questionnaire).

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 the number of missing data will be given and the following descriptive statistics will be provided:

- For quantitative parameters: mean, standard deviation, 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 **one-sided tests**.

The statistical results are conclusive for the primary efficacy criterion.

All the other 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 and missing data (other than WURSS-21 questionnaire and dates)

Concerning dates and WURSS-21 questionnaire, see §6.4.

No imputation will be done. Missing data will not be estimated and will be treated as missing data for the statistical analysis.

c) Dropouts

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

Except for WURSS-21 questionnaire and dates, no method will be applied to replace missing data.

6.4. General conventions and 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 inclusion visit and 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, it will be estimated by the reference end date
- If the month/year < month/year of reference end date, it will be estimated by the last day of the month
- If the month/year > month/year of reference end date, 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.

6.4.6. Scores of WURSS-21 questionnaire

To compute scores of WURSS-21 questionnaire, if the questionnaire has been completed at a given time point except some items, these missing answers will be imputed by the last observation carried forward (LOCF).

At time-points the questionnaire has not been completed at all, no imputation will be done and the scores will be missing.

6.4.7. AUC on scores of WURSS-21 questionnaire

The computation of the AUC on any score of the questionnaire will be made for patients with non-missing value at D1 and at least another non-missing time point between D2 and D8. Otherwise, the AUC will be missing.

The AUC will be computed by the trapezoidal rule from D1 to D8 (Acute Phase).

If the value at D8 is missing, then it will be estimated by the value at the last non-missing time point before D8.

7. STUDY PATIENTS

7.1. Disposition of patients

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 by treatment group and overall.
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 Per-Protocol Set.

Major deviations are defined by:

- Non-compliance with the inclusion or exclusion criteria;
- No assessment of the primary efficacy criterion (WURSS-21) at D1, D4±1 and D8-1 during the treatment period;
- Intake of forbidden medication, i.e. local or systemic corticosteroids, non-steroidal anti-inflammatory drugs (NSAID) or saline nasal spray;
- Intake of wrong treatment, i.e. wrong treatment given to the patient after randomization;
- A compliance to study product intake below 80% or greater than 120%.

All other deviations will a priori be considered as minor, e.g.:

- Telephone call or V2's dates that do not conform with the flow chart of the study;
- Telephone call or V2 not performed;
- Daily phone call to the subjects (in case of WURSS-21 non-completion) not performed (between D1 and D8);
- Treatment stopped before or after D8 morning (less or more than 14 intakes of study product);
- Non-compliance regarding the informed consent form;
- WURSS data missing (but data available at D1, D4±1 and D8-1) until subject's recovery (two consecutive and negative – "not sick" – answers to the first item) or D15/subject's end of study, whichever occurs first.

Major and minor deviations and their types will be described by treatment group and overall.
They will be summarised with frequencies and percentages.
Subjects will be counted only once within each type of deviation and within each category (major/minor).
A listing of all deviations will be provided for all included subjects, including the category.

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

All demographic and baseline characteristics will be described on the Safety Set, by treatment group and overall.

8.1. Demographic characteristics

Age (years) and sex will be summarised using descriptive statistics already mentioned in §6.2.

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 and are classified by System Organ Class and Preferred Term.

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

Subjects will be counted only once within these categories.

8.4. Symptom's score of acute rhinitis

Symptoms' scores of acute infectious rhinitis will be described at baseline.
For each symptom's score, a Student (or Wilcoxon if the normality assumption is not acceptable) between-groups test will be performed.

8.5. Total Score of WURSS-21 at baseline

Total score of WURSS-21 (the sum of the scores of the twenty first items of the WURSS-21 questionnaire) will be described at baseline.
A Student (or Wilcoxon if the normality assumption is not acceptable) between-groups test will be performed.

8.6. COVID-19 antigen test at baseline

The results in each group of the COVID-19 antigen test performed at baseline will be described and compared by means of chi-square or exact Fisher test.

9. COMPLIANCE

Compliance will be calculated according to the following formula and analysed on the Safety set, by treatment group and overall.

The compliance will be calculated as follows:

Compliance (%) = [Initial weight of the container (g) – Real weight of the container at the end of the study (g)] × 100 / [Initial weight of the container (g) – Theoretical weight of the container at the end of complete study (g)]

with:

- Initial weight of the container = 33g;
- Theoretical weight of the container at the end of complete study = 27.7g;

i.e.:

$$\boldsymbol{Compliance}\ (\%) = \frac{(\mathbf{33} - \boldsymbol{weight_{end}}) \times \mathbf{100}}{\mathbf{5.3}}$$

with $weight_{end}$ the real weight of the container at the end of the study in g.

10. EFFICACY

10.1. Analysis of the primary efficacy criterion

The primary objective will be analysed by performing a t-test (or a Wilcoxon test if the normality assumption is not acceptable) on the means of AUC of total WURSS-21 score during first eight days of symptoms between treatment groups.

The answers of the twenty first items of the WURSS-21 questionnaire are scored **from 0 to 7** (0: negative answer; from 1 to 7: positive answer with an increasing severity level). See the daily symptom report in appendix (§13.3).
The total WURSS-21 score at each time point is the sum of the scores of the twenty first items of the WURSS-21 questionnaire:

$$\text{At each time point t: } \mathbf{WURSS_{TOT}(t)} = \sum_{j \text{ in } \{1;\ ...;\ 20\}} \mathbf{WURSS_j(t)}$$

AUC of total WURSS-21 score will be computed by the method described in §6.4.7.

At time points the questionnaire has been completed, possible unanswered items will be imputed by the method described in §6.4.6.

Subjects will be analysed on the Full Analysis Set and the Per-Protocol Set. In each case, boxplots of the AUC on total score will be realized by treatment group. The number of available data and the p-value will be printed on the figure.

10.2. Analysis of the secondary efficacy criteria

10.2.1. AUC for each of the WURSS-21 components (symptoms and Quality-of-Life)

For the symptoms' and Quality-of-Life's scores of the WURSS-21 questionnaire, the AUC will be computed by the method described in §6.4.7 and a t-test (or a Wilcoxon test if the normality assumption is not acceptable) will be performed on the means of AUC during first eight days of symptoms between treatment groups.

The symptoms' WURSS-21 score at each time point is the sum of the items 2 to 11 of the WURSS-21 questionnaire:

$$\text{At each time point t: } \mathbf{WURSS_{symptoms}(t)} = \sum_{j \text{ in } \{2;\ ...;\ 11\}} \mathbf{WURSS_j(t)}$$

The Quality-of-Life's WURSS-21 score at each time point is the sum of the items 12 to 20 of the WURSS-21 questionnaire:

$$\text{At each time point t: } \mathbf{WURSS_{QoL}(t)} = \sum_{j \text{ in } \{12;\ ...;20\}} \mathbf{WURSS_j(t)}$$

At time points the questionnaire has been completed, possible unanswered items will be imputed by the method described in §6.4.6.

Subjects will be analysed on the Full Analysis Set and the Per-Protocol Set. In each case, boxplots of both AUC on symptoms' and Quality-of-Life's scores will be realized by treatment group. Numbers of available data and p-values will be printed on the figure.

10.2.2. Impact of the treatment on the cold symptoms' duration

Hereinafter, the "recovery date" is the first day of two last days the patient answered to the WURSS-21 questionnaire. The patient must have reported a negative answer to the question 1 ("not sick") and the two last days must be consecutive. Otherwise, there is no "recovery date" for the patient.

For the items 2 to 11 of WURSS-21 questionnaire, the duration of the corresponding symptom is defined as the duration between first symptomatic day and last symptomatic day.

Cold symptom's duration (days) = Last symptomatic day – first symptomatic day + 1

For a given symptom, a symptomatic day is a day the patient gave an answer other than negative to the corresponding question ("do not have this"). Missing answers will be imputed by the LOCF.

The considered symptomatic days are between D1 and either D15, or the end of the study, or the day before the recovery date, whichever occurs first. Symptomatic days from the recovery date will not be taken into account.

For each of the items 2 to 11 of the WURSS-21 questionnaire, the origin date will be the date of the first symptomatic day.

The considered event is the end of the symptom.

For patients who reported a negative answer to the corresponding question on the last day they answered to it, or for patients with a recovery date, the event date will be the last symptomatic day before his/her last day of completion of the questionnaire, or before the recovery date if it exists.

Patients who did not report a negative answer to the corresponding question on the last day they answered to it, and without recovery date, will be censored at D15 or at the end of the study, and the censoring date will be the date of D15 or the reference end date, whichever occurs first.

For patients who never reported the presence of a given symptom (never ticked "very mild", "mild", "moderate" or "severe") and having completed the questionnaire at D1, the origin date for the symptom will be D1, the symptom will be censored at D1 and the corresponding duration will be zero. If patients who never reported the presence of a given symptom did not complete the questionnaire at D1, neither origin date nor censoring date will be defined for this symptom and the corresponding duration will be missing.

For each of the items 2 to 11 of the WURSS-21 questionnaire, duration endpoints will be summarized using the medians, with 95% confidence intervals (CIs) for the medians by group. Results for Healsea® Rescue* group and Placebo group will be compared using Wilcoxon-Mann-Whitney test. Subjects will be analysed on the FAS.

For each duration, boxplots will be realized by treatment group. Numbers of available data and p-values will be printed on the figure.

10.2.3. Number of days of use of concomitant treatments in each group

The number of days of use of concomitant treatments, that may affect common cold symptoms, in each group will be compared by means of chi-square or exact Fisher test. Subjects will be analysed on the FAS.

The treatments that may affect common cold symptoms are antipyretics, systemic or local mucolytics, decongestants, antitussives and antibiotics.

The number of days of use of these medications is defined as follows:

- A day is counted when the patient used at least one of these medications this day;
- Each day is counted once, whatever the number of these medications used this day;
- The total number is the sum of all distinct days of use of these medications, from D1 to D15.

The same analysis will be performed for each category of medications: antipyretics, systemic or local mucolytics, decongestants, antitussives and antibiotics.

10.2.4. Subject general satisfaction in each group

The subject general satisfaction regarding ease of use, local tolerance and taste and efficacy at V2 in each group will be compared by means of chi-square or exact Fisher test for each of the three items.

The global subject feedback on treatment use (“will you recommend the prescribed treatment for treatment of acute rhinitis?”) in each group will be compared by means of chi-square or exact Fisher test.

Subjects will be analysed on the FAS.

10.3. 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. They will be analysed on the FAS.

Note: a medication which began before the reference start date and which is ongoing after the reference start date is counted in "previous medications" (see §8.2) and not in "concomitant medications".

10.4. Non-related adverse events

In the following paragraph, for a smoother reading:

- adverse events will be referred as AE;
- treatment-emergent adverse events will be referred as TEAE.

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

For efficacy analyses, only non-related AEs are considered, i.e. adverse events with a relationship to study device equal to "not related". These analyses will be performed on the Safety Set.

An adverse event will be considered as a treatment-emergent adverse event (TEAE) if:

- it was reported at least one day after screening;
- it was not 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 start date).

Missing or incomplete dates will be estimated as described in §6.4.4 in order to determine the TEAEs, but they will be presented as reported in CRF in the data listings. Generally, an adverse event 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.

Note: if the intensity/severity is missing, a conservative approach will be adopted and the intensity/severity will be considered as severe.

A given treatment-emergent adverse event (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.

- Summary of non-related adverse events

A summary table will be produced:

- number and percentage of subjects with at least one non-related adverse event (AE);
- number and percentage of subjects with at least one non-related AE leading to definitive study device discontinuation;
- number and percentage of subjects with at least one non-related AE leading to definitive study discontinuation;
- number and percentage of subjects with at least one non-related TEAE.

The number of non-related AEs of each category will also be provided in this table.

- Analysis of non-related treatment-emergent adverse event

The number and percentage of subjects with non-related TEAEs will be summarised by System Organ Class and Preferred term.

The number of non-related TEAEs of each category will also be provided in this table.

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

11. SAFETY

The following analyses will be performed on the Safety Set.

11.1. Study duration

Study duration will be calculated according to the formula below:

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

It will be described (see §6.2) on the Safety Set.

11.2. Incidents and expected side effects

For safety analyses, only incidents and expected side effects are considered, i.e. adverse events with a relationship to study device other than "not related".

- Summary of incidents

A summary table will be produced:
- number and percentage of subjects with at least one incident;
- number and percentage of subjects with at least one incident leading to definitive study device discontinuation;
- number and percentage of subjects with at least one incident leading to definitive study discontinuation;
- number and percentage of subjects with at least one serious incident.

The number of incidents of each category will also be provided in this table.

- Analysis of incident

The number and percentage of subjects with incidents will be summarised by System Organ Class (SOC) and Preferred term (PT).

The number of incidents of each category will also be provided in this table.

A listing of serious incidents will be provided if applicable.

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

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

The cold symptoms' duration was defined in the protocol as the number of symptomatic days between D1 and the first day the subject reports not having the symptom for two consecutive days.
Furthermore, since several patients still reported having symptoms while they reported they did not feel sick anymore at the question 1 during the two last days of completion of the WURSS-21 questionnaire, their positive answers to the cold symptoms' items have been considered as non-significant. Consequently, the question 1 has been taken into account instead of the corresponding items to determine the end of the cold symptoms' duration, however only on the condition that the two last days of completion were consecutive.
If the two last days of completion were not consecutive, positive answers to cold symptoms' items are still considered as symptomatic, even if the two last answers to the question 1 are negative. The symptom ends at the last symptomatic day if the patient reported the absence of this symptom after this day. Otherwise, the duration of the symptom is censored at D15 or at the end of the study, whichever occurs first.

13. APPENDICES

13.1. List of statistical tables, figures and listings

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STUDY SUBJECTS		
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Table	14.2.1.1	AUC on total WURSS-21 score per treatment group – Full Analysis Set
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Figure	14.2.1.1	Boxplots of AUC on total WURSS-21 score by treatment group – Full Analysis Set
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Table	14.2.2.1.1	AUC for each of the WURSS-21 components (symptoms and Quality-of-Life) scores per treatment group – Full Analysis Set
Table	14.2.2.1.2	AUC for each of the WURSS-21 components (symptoms and Quality-of-Life) scores per treatment group – Per-Protocol Set
Figure	14.2.2.1.1	Boxplots of AUC on symptoms' and Quality-of-Life's WURSS-21 scores by treatment group – Full Analysis Set

Type	Number	Title
Figure	14.2.2.1.2	Boxplots of AUC on symptoms' and Quality-of-Life's WURSS-21 scores by treatment group – Per-Protocol Set
Table	14.2.2.2	Impact of the treatment on the cold symptoms' duration – Full Analysis Set
Figure	14.2.2.2	Boxplots of the cold symptoms' durations by treatment group – Full Analysis Set
Table	14.2.2.3.1	Number of days of use of concomitant treatments that may affect common cold symptoms in each group – Full Analysis Set
Table	14.2.2.3.2	Number of days of use of antipyretics in each group – Full Analysis Set
Table	14.2.2.3.3	Number of days of use of systemic/local mucolytics in each group – Full Analysis Set
Table	14.2.2.3.4	Number of days of use of decongestants in each group – Full Analysis Set
Table	14.2.2.3.5	Number of days of use of antitussives in each group – Full Analysis Set
Table	14.2.2.3.6	Number of days of use of antibiotics in each group – Full Analysis Set
Table	14.2.2.4	Subject general satisfaction in each group – Full Analysis Set
Table	14.2.3	Concomitant treatments – Full Analysis Set
Table	14.2.4.1.1	Summary of non-related adverse events – Safety Set
Table	14.2.4.1.2	Non-related treatment-emergent adverse events by System Organ Class and Preferred Term – Safety Set
Listing	14.2.4.2.1	Listing of non-related adverse events leading to definitive discontinuation of the trial device – Safety Set (if applicable)
Listing	14.2.4.2.2	Listing of non-related adverse events leading to definitive discontinuation of the study – Safety Set (if applicable)
SAFETY – INCIDENTS		
Table	14.3.1.1	Summary of incidents – Safety Set
Table	14.3.1.2	Related treatment-emergent adverse events by System Organ Class and Preferred Term – Safety Set
Listing	14.3.2.1	Listing of serious incidents – Safety Set (if applicable)
Listing	14.3.2.2	Listing of incidents leading to definitive discontinuation of the trial device – Safety Set (if applicable)
Listing	14.3.2.3	Listing of incidents leading to definitive discontinuation of the study – Safety Set (if applicable)
SUBJECTS DATA LISTINGS		
Listing	16.2.1.1	Subjects discontinued from the study after enrolment
Listing	16.2.2.1	Subjects with protocol deviations
Listing	16.2.3.1	Subjects' disposition and analysis sets

Type	Number	Title
Listing	16.2.4.1	Demographic characteristics by subject
Listing	16.2.4.2	Medical history by subject
Listing	16.2.4.3	Symptoms of acute infectious rhinitis
Listing	16.2.4.4	Inclusion/Exclusion criteria
Listing	16.2.5.1	Dates of visits
Listing	16.2.5.2	Compliance to Healsea Rescue intake
Listing	16.2.6.1	Questionnaire WURSS-21
Listing	16.2.6.2	Previous and concomitant medications by subject
Listing	16.2.6.3	Patients' satisfaction questionnaire
Listing	16.2.7.1	Adverse events, incidents and expected side effects
Listing	16.2.8.1	COVID-19 antigen tests

13.2. Mock tables

Table 14.1.1.1. Subjects' disposition – Screened subjects

	Healsea Rescue N=XX	Placebo N=XX	Total N=XX
Analysis Sets			
Screened subjects	XX (100.0%)	XX (100.0%)	XX (100.0%)
Included subjects	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Randomised subjects	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Safety Set	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Full Analysis Set	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Per-Protocol Set	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

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

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

Figure 14.1.1.1. Subjects' disposition – Screened subjects

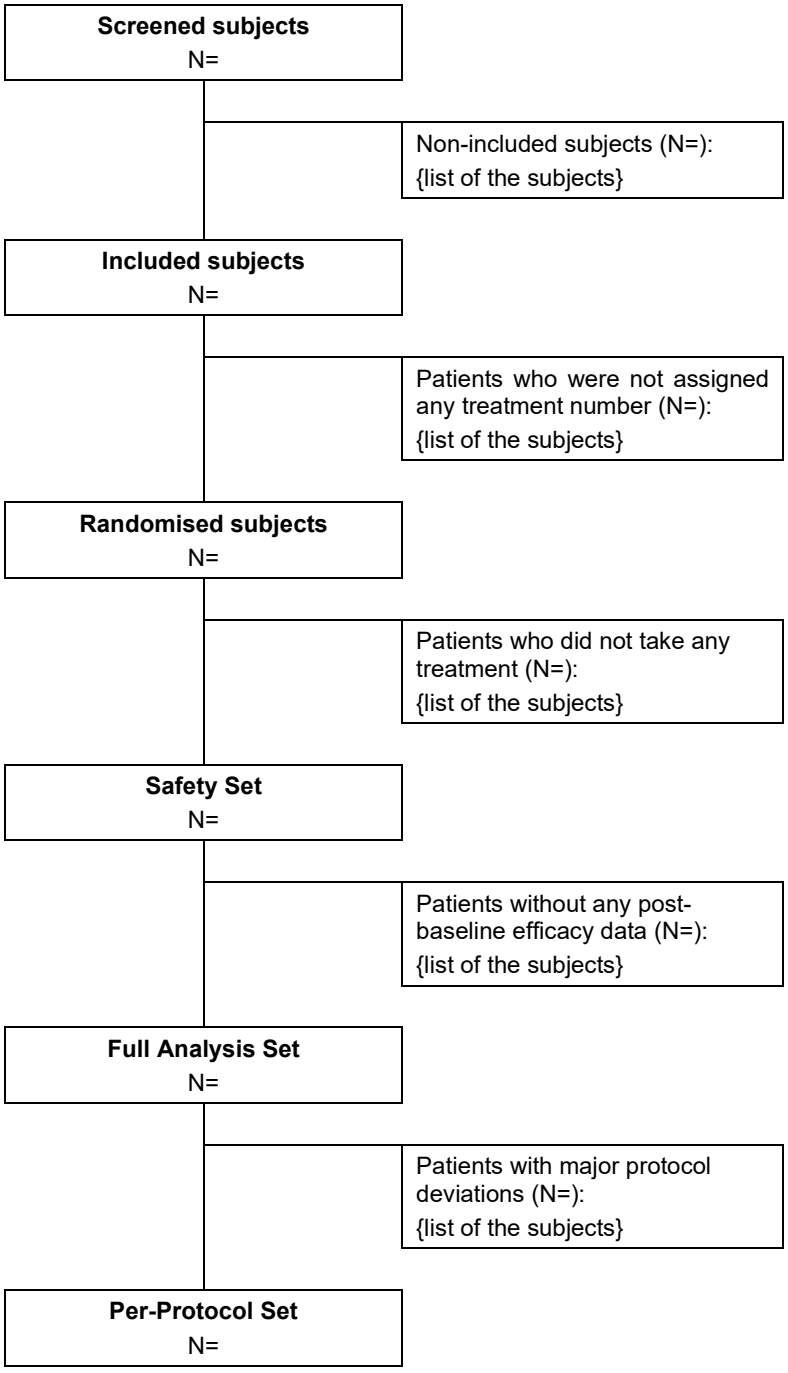

Table 14.1.1.2.1. Summary of protocol deviations by category and type – Included subjects

Category of deviation – Type of deviation	Healsea Rescue N=XX	Placebo N=XX	Total N=XX
Subjects with at least one protocol deviation			
All	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Major deviations			
All	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
XXXXX	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
XXXXX	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Minor deviations			
All	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
XXXXX	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
XXXXX	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Listing 14.1.1.2.1. Subjects with at least one protocol deviation – Included subjects

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

Table 14.1.1.2.2. Premature withdrawal – Reason of withdrawal

	Healsea Rescue N=XX	Placebo N=XX	Total N=XX
Reason of premature withdrawal			
XXXXXXX	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Listing 14.1.1.2.2. Subjects prematurely withdrawn – Included subjects

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

Table 14.1.2.1. Demographic characteristics – Safety Set

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

Table 14.1.2.2. Summary of previous and concomitant medications at baseline – Safety Set

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

Table 14.1.2.3. Medical and surgical past history – Safety Set

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

Table 14.1.2.4. Symptoms of acute infectious rhinitis at baseline – Safety Set

	Healsea Rescue N=XX	Placebo N=XX	Total N=XX
XXXXX score			
N	XX	XX	XX
Missing	XX	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median	XX	XX	XX
Q1/Q3	XX / XX	XX / XX	XX / XX
Min/Max	XX / XX	XX / XX	XX / XX
Between-groups test	XXX (Student/Wilcoxon)		
Total score			
N	XX	XX	XX
Missing	XX	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median	XX	XX	XX
Q1/Q3	XX / XX	XX / XX	XX / XX
Min/Max	XX / XX	XX / XX	XX / XX
Between-groups test	XXX (Student/Wilcoxon)		

Table 14.1.2.5. Total WURSS-21 score at baseline – Safety Set

	Healsea Rescue N=XX	Placebo N=XX	Total N=XX
Total WURSS-21 score			
N	XX	XX	XX
Missing	XX	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median	XX	XX	XX
Q1/Q3	XX / XX	XX / XX	XX / XX
Min/Max	XX / XX	XX / XX	XX / XX
Between-groups test	XXX (Student/Wilcoxon)		

Table 14.1.2.6. Results of the COVID-19 antigen test at baseline – Safety Set

	Healsea Rescue N=XX	Placebo N=XX	Total N=XX
COVID-19 antigen test			
N	XX	XX	XX
Missing	XX	XX	XX
Negative	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Positive	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Between-groups test	XXX (Chi-2/Fisher)		

Table 14.1.3. Summary of compliance per treatment group – Safety Set

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

Table 14.1.4. Study duration by subject – Safety Set

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

Table 14.2.1.2. AUC on total WURSS-21 score per treatment group – Per-Protocol Set

	Healsea Rescue N=XX	Placebo N=XX	Total N=XX
AUC on total WURSS-21 score			
N	XX	XX	XX
Missing	XX	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median	XX	XX	XX
Q1/Q3	XX / XX	XX / XX	XX / XX
Min/Max	XX / XX	XX / XX	XX / XX
Between-groups test	XXX (Student/Wilcoxon)		

Table 14.2.2.1.2. AUC for each of the WURSS-21 components (symptoms and Quality-of-Life) scores per treatment group – Per-Protocol Set

	Healsea Rescue N=XX	Placebo N=XX	Total N=XX
AUC on symptoms' WURSS-21 score			
N	XX	XX	XX
Missing	XX	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median	XX	XX	XX
Q1/Q3	XX / XX	XX / XX	XX / XX
Min/Max	XX / XX	XX / XX	XX / XX
Between-groups test	XXX (Student/Wilcoxon)		
AUC on Quality-of-Life's WURSS-21 score			
N	XX	XX	XX
Missing	XX	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median	XX	XX	XX
Q1/Q3	XX / XX	XX / XX	XX / XX
Min/Max	XX / XX	XX / XX	XX / XX
Between-groups test	XXX (Student/Wilcoxon)		

Table 14.2.2.1. Impact of the treatment on the cold symptoms' duration – Full Analysis Set

	Healsea Rescue N=XX	Placebo N=XX
XXX – Duration (days)		
N	XX	XX
Missing	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Median [95%CI]	XX.X [XX.X; XX.X]	XX.X [XX.X; XX.X]
Q1/Q3	XX / XX	XX / XX
Min/Max	XX / XX	XX / XX
p-value (Wilcoxon)	XXX	

Figure 14.2.X.X. Boxplots of XXX by treatment group – XXX Set

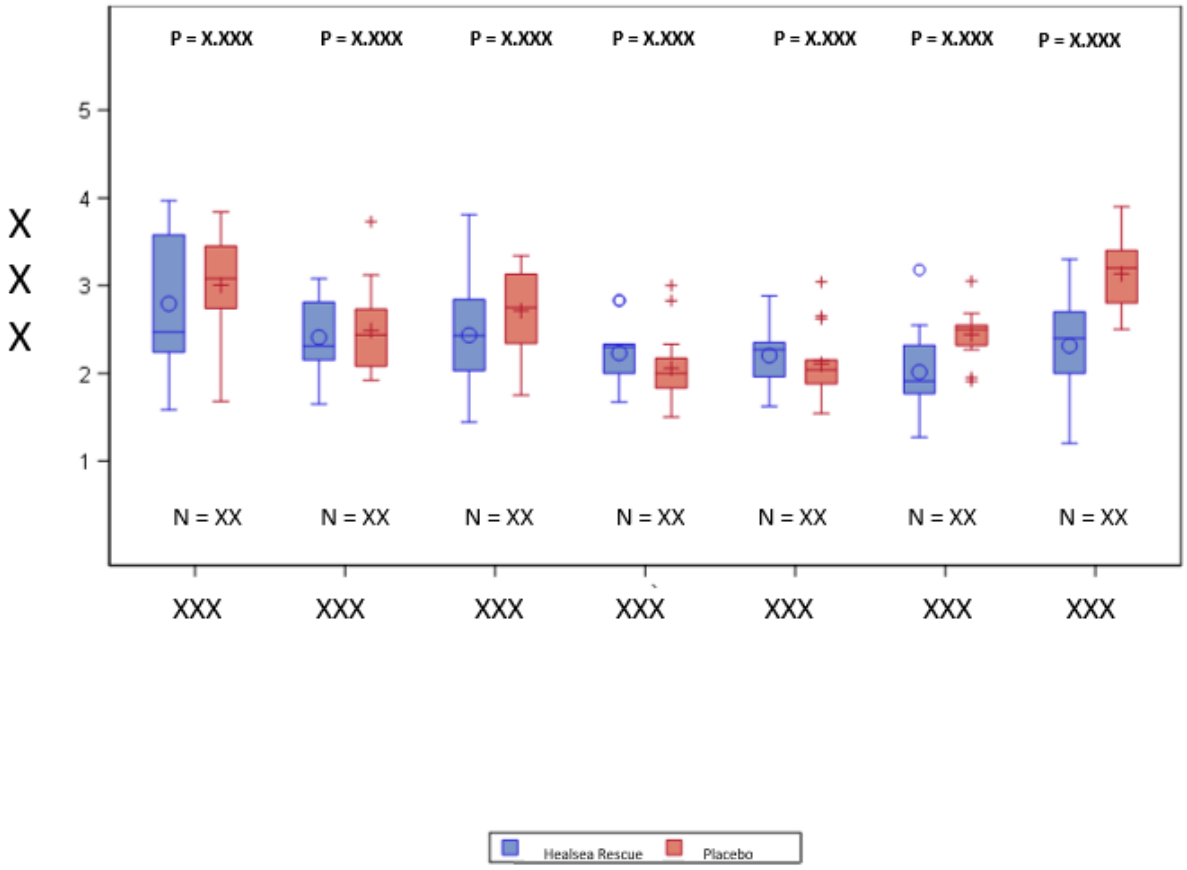

Table 14.2.2.3.X. Number of days of use of XXX in each group – Full Analysis Set

	Healsea Rescue N=XX	**Placebo N=XX**
Number of days of intakes of XXX		
N	XX	XX
Missing	XX	XX
0	XX.X (XX.X%)	XX.X (XX.X%)
1	XX.X (XX.X%)	XX.X (XX.X%)
2	XX.X (XX.X%)	XX.X (XX.X%)
…	XX.X (XX.X%)	XX.X (XX.X%)
Between-groups test	XXX (Chi-2/Fisher)	

Table 14.2.2.4. Subject general satisfaction in each group – Full Analysis Set

	Healsea Rescue N=XX	**Placebo N=XX**
How would you characterize the use of the nasal spray?		
N	XX	XX
Missing	XX	XX
Not easy	XX (XX.X%)	XX (XX.X%)
Pretty easy	XX (XX.X%)	XX (XX.X%)
Easy	XX (XX.X%)	XX (XX.X%)
Very easy	XX (XX.X%)	XX (XX.X%)
Between-groups test	XXX (Chi-2/Fisher)	
How would you characterize the residual taste after spraying the prescribed treatment?		
N	XX	XX
Missing	XX	XX
Not pleasant	XX (XX.X%)	XX (XX.X%)
Neutral	XX (XX.X%)	XX (XX.X%)
Pleasant	XX (XX.X%)	XX (XX.X%)
Very pleasant	XX (XX.X%)	XX (XX.X%)
Between-groups test	XXX (Chi-2/Fisher)	
How would you characterize the cleansing and moistening of nasal mucosa with the prescribed treatment?		
N	XX	XX
Missing	XX	XX
No improvement	XX (XX.X%)	XX (XX.X%)
Slight improvement	XX (XX.X%)	XX (XX.X%)
Moderate improvement	XX (XX.X%)	XX (XX.X%)
Very clear improvement	XX (XX.X%)	XX (XX.X%)
Between-groups test	XXX (Chi-2/Fisher)	
Will you recommend the prescribed treatment for treatment of acute rhinitis?		
N	XX	XX
Missing	XX	XX
No	XX (XX.X%)	XX (XX.X%)
Yes	XX (XX.X%)	XX (XX.X%)
Between-groups test	XXX (Chi-2/Fisher)	

Table 14.2.3. Concomitant treatments – Full Analysis Set

ATC1 - ATC2	Healsea Rescue N=XX	Placebo N=XX	Total N=XX
Subjects with at least one concomitant medication			
All	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
XXXXX			
All	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
XXXXX	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
XXXXX	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table 14.2.4.1.1. Summary of non-related adverse events – Safety Set

	Healsea Rescue N=XX		Placebo N=XX		Total N=XX	
	n (%)	[E]	n (%)	[E]	n (%)	[E]
Number and percentage of subjects with non-related / Number of non-related						
Adverse event	XX (XX.X%)	XXX	XX (XX.X%)	XXX	XX (XX.X%)	XXX
Adverse event leading to definitive study device discontinuation	XX (XX.X%)	XXX	XX (XX.X%)	XXX	XX (XX.X%)	XXX
Adverse event leading to definitive study discontinuation	XX (XX.X%)	XXX	XX (XX.X%)	XXX	XX (XX.X%)	XXX
Treatment-emergent adverse event	XX (XX.X%)	XXX	XX (XX.X%)	XXX	XX (XX.X%)	XXX

Table 14.2.4.1.2. Non-related treatment-emergent adverse events by System Organ Class and Preferred Term – Safety Set

SOC - Preferred Term	Healsea Rescue N=XX		Placebo N=XX		Total N=XX	
	n (%)	[E]	n (%)	[E]	n (%)	[E]
Non-related treatment-emergent adverse events						
All	XX (XX.X%)	XXX	XX (XX.X%)	XXX	XX (XX.X%)	XXX
XXXXX						
All	XX (XX.X%)	XXX	XX (XX.X%)	XXX	XX (XX.X%)	XXX
XXXXX	XX (XX.X%)	XXX	XX (XX.X%)	XXX	XX (XX.X%)	XXX
XXXXX	XX (XX.X%)	XXX	XX (XX.X%)	XXX	XX (XX.X%)	XXX

Listing 14.2.4.2.X Listing of XXXX – Safety Set

ID – Sex – Age	Treatment	Non-related adverse event	Start date / end date	Ongoing at the end of the study	Intensity	Serious	Action taken

Table 14.3.1.3. Summary of incidents – Safety Set

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

Table 14.3.1.4. Incidents by System Organ Class and Preferred Term – Safety Set

	Healsea Rescue N=XX		Placebo N=XX		Total N=XX	
SOC - Preferred Term	n (%)	[E]	n (%)	[E]	n (%)	[E]
Incidents						
All	XX (XX.X%)	XXX	XX (XX.X%)	XXX	XX (XX.X%)	XXX
XXXXX						
All	XX (XX.X%)	XXX	XX (XX.X%)	XXX	XX (XX.X%)	XXX
XXXXX	XX (XX.X%)	XXX	XX (XX.X%)	XXX	XX (XX.X%)	XXX
XXXXX	XX (XX.X%)	XXX	XX (XX.X%)	XXX	XX (XX.X%)	XXX

Listing 14.3.2.X Listing of XXXX – Safety Set

ID – Sex – Age	Treatment	Incident	Start date / end date	Ongoing at the end of the study	Intensity	Serious	Action taken	Causality

13.3. WURSS-21 questionnaire – Daily symptom report

Please complete the WURSS -21 in **the evening**, taking in account the symptoms from the morning to the evening, until you do not feel sick during two consecutive days (first question ticked NO during 2 consecutive days). In the case you already ticked "not sick" for 2 consecutive days during the TREATMENT PERIOD (D1 to Day 8), please do not complete the questionnaire either.

Please fill in one circle for each of the following items:

	Not sick	Very mildly		Mildly		Moderately		Severely
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
How sick do you feel **today**?	O	O	O	O	O	O	O	O

Please rate the **average severity of your cold symptoms over the last 24 hours** for each symptom:

	Do not have this symptom	Very mild		Mild		Moderate		Severe
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Runny nose	O	O	O	O	O	O	O	O
Plugged nose	O	O	O	O	O	O	O	O
Sneezing	O	O	O	O	O	O	O	O
Sore throat	O	O	O	O	O	O	O	O
Scratchy throat	O	O	O	O	O	O	O	O
Cough	O	O	O	O	O	O	O	O
Hoarseness	O	O	O	O	O	O	O	O
Head congestion	O	O	O	O	O	O	O	O
Chest congestion	O	O	O	O	O	O	O	O
Feeling tired	O	O	O	O	O	O	O	O

Over the last 24 hours, how much has your cold interfered with your ability to:

	Not at all	Very mildly		Mildly		Moderately		Severely
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Think clearly	O	O	O	O	O	O	O	O
Sleep well	O	O	O	O	O	O	O	O
Breathe easily	O	O	O	O	O	O	O	O
Walk, climb stairs, exercise	O	O	O	O	O	O	O	O
Accomplish daily activities	O	O	O	O	O	O	O	O
Work outside the home	O	O	O	O	O	O	O	O
Work inside the home	O	O	O	O	O	O	O	O
Interact with others	O	O	O	O	O	O	O	O

Live your personal life	O	O	O	O	O	O	O	O

Compared to yesterday, I feel that my cold is…

Very much better	Somewhat better	A little better	The same	A little worse	Somewhat worse	Very much worse
O	O	O	O	O	O	O