STATISTICAL ANALYSIS PLAN

Healsea Children
- PMCF study -

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APPROVAL OF THE STATISTICAL ANALYSIS PLAN

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LIST OF ABBREVIATIONS

AE:	Adverse Event
ANCOVA:	Analysis of covariance
ATC:	Anatomical Therapeutic Chemical Classification
AUC:	Area Under the Curve
CRF:	Case Report Form
CRO:	Contract Research Organisation
FAS:	Full Analysis Set
IgE:	Immunoglobulin E
LOCF:	Last Observation Carried Forward
MedDRA:	Medical Dictionary for Regulatory Activities
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
WHO-DRUG:	World Health Organization Drug Dictionary
WURSS-K:	Wisconsin Upper Respiratory Symptom Survey for Kids

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1. INTRODUCTION

This statistical analysis plan is based on clinical investigation plan LPH-2101 – version 2, dated on September 8th, 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 assess the impact of both treatment modalities (Healsea® Children on top of common cold conventional therapies and common cold conventional therapies only) to reduce acute infectious rhinitis symptoms in 6-10 years old allergic children during a 10-day treatment period.

2.2. Secondary objectives

The secondary objectives are:
- To assess the impact of both treatment modalities to reduce the duration of each infectious rhinitis symptom as rated by the Wisconsin Upper Respiratory Symptom Survey for Kids (WURSS-K).
- To assess the impact of both treatment modalities to reduce complications of the acute phase during a 20-day follow-up phase.
- To assess the impact of both treatment modalities on the intake of conventional common cold medication (antibiotics, antipyretics, mucolytics, decongestants, antitussives, systemic and topical corticosteroids).
- To assess the impact of both treatment modalities to reduce the person to person spreading among close contacts (parents, siblings).
- Safety: to assess systemic and local tolerance of Healsea® Children over the study period.

3. STUDY DESIGN

This is a prospective, open label, interventional, national (Poland), multicentric study.
During this prospective interventional study, one cohort of IgE-dependent allergic children with early symptoms of infectious rhinitis will be followed, children being treated with Healsea® Children on top of common cold conventional therapies or with conventional therapies only (nasal irrigation excepted). This study aimed to confirm the benefit of Healsea® Children in a real life setting in children with perennial allergy.

Investigational plan description (see Figure 1):

- **Visit 1 (V1) – (Day 1): Screening/Inclusion**
  Information and provision of the information sheet to legal guardians and participants, consent and assent signatures, demographic data and medical history, ongoing medication, physical and clinical examination, inclusion/non-inclusion criteria, record of patient choice regarding Healsea® Children use.
- **D1-D10 (at home):**

Daily completion of the electronic diary (WURSS-K, adverse events/incident/ undesirable expected side effects and concomitant medications, contamination of relatives if applicable, Healsea® Children daily administration if applicable).

– **D5±2 (at home): Telephone call 1**

Investigator/nurse call to review patient status and study progress, adverse event/incident/undesirable expected side effects and concomitant treatments.

– **Visit 2 (V2) – (Day 10±2): End of treatment**

End of Healsea® Children nasal spray treatment if applicable, assessment of symptoms, diary review, reporting of adverse events/incident/undesirable expected side effects.

– **D11-D30±5 (at home):**

Daily completion of the diary (Adverse event, concomitant medications, contamination of relatives if applicable, WURSS-K if applicable, until the subject feels not sick for two consecutive days).

– **D20±2 (at home): Telephone call 2**

Investigator/nurse call to review patient status and study progress, adverse events and concomitant treatments.

– **Visit 3 (V3) – (Day 30±5): End of study**

Physical and clinical examination, diary review, reporting of adverse events and concomitant treatments

The maximal study duration for each subject is 35 days.

	ACUTE PHASE				FOLLOW-UP		
Visit name	Screening/Inclusion	At home	Telephone call	End of treatment	At home	Telephone call	End of study
Visit Number	V1		TC1	V2		TC2	V3
Days/Weeks	D1	D1 – D10	D5±2	D10±2	D11 – D30±5	D20±2	D30 ± 5
Screening and General Assessments							
Information and consent process	X						
Eligibility criteria	X						
Demography and Medical history	X						
Physical and clinical examination	X			X			X
Ongoing medication	X						
Patient's choice for using Healsea® Children self-administration or not	X						
Treatment							
Acute phase (Healsea® Children or no saline irrigation as add on therapy)		X					
Assessments							
Subject e-diary (WURSS-K)		X			X*		
Adverse Events/incidents/undesirable expected side effects and concomitant medication reporting	X	X	X	X	X	X	X

* After D10, the WURSS-K will be assessed once daily until the subject feels not sick for two consecutive days if applicable.

Figure 1 : Flow chart of the study

4. SAMPLE SIZE

An arbitrary cohort of 200 children has been chosen. A cohort of 100-exposed and 100-not exposed patients is anticipated to allow to demonstrate the interest of using Healsea® Children in the allergic paediatric population.
Indeed, 100 patients by arms are enough to detect a Cohen's effect size of 0.4 with a power of 80% and a type I error of 5%. Cohen's effect size is defined as the standardized difference between AUC in groups. Following Cohen's methodology, 0.4 is an intermediate size between a small effect (0.2) and a medium effect (0.5) and is coherent with the expected result.

5. DEFINITION OF THE ANALYSIS SETS

Screened subjects: all subjects who signed an informed consent.

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

Full Analysis Set (FAS): all included subjects who used the investigational medical device at least once.

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

Safety and Efficacy analyses will be performed on the FAS.
The analyses of the primary and one secondary (modelling of AUC on total WURSS by multivariate ANCOVA) efficacy criteria will also be performed on the PP Set.

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, 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.

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-K questionnaire and dates)

Concerning dates and WURSS-K 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-K 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. AUC on total score of WURSS-K questionnaire

The computation of the AUC will be made for patients with non-missing value at D1 and at least another non-missing time point between D2 and D11. Otherwise, the AUC will be missing.

The AUC will be computed by the trapezoidal rule from D1 to D10 (Acute Phase).

If the value at D10 is missing:

- If there is no follow-up for the patient or if the value at D11 (the first day of Follow-up) is missing, then the value at D10 will be estimated by the value at the last non-missing time point before D10;
- If the value at D11 is not missing, the value at D10 will be estimated by a linear regression between the last non-missing time point before D10, noted Dj, and D11:

$$\mathbf{WURSS_{TOT,\,EST}(D10) = [WURSS_{TOT}(Dj) + (10 - j) \times WURSS_{TOT}(D11)] / (11 - j)}$$

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 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-K) at D1, D5±1 and D10±1 during the treatment period;
- Intake of forbidden medication, i.e. nasal irrigation for patient who chose to not take Healsea® Children.

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

- Visits' dates not conform to the flow chart of the study;
- Compliance of the product Healsea® Children (see §9) not between 80% and 120%.

Major and minor deviations will be described by treatment group and overall. A listing of all deviations will be provided for all included subjects, including the type (major/minor).

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 FAS, by treatment group and overall.

8.1. Demographic characteristics

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

Age (years) = (reference start date – date of birth) / 365.25 *(truncated 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 2021 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 20.1 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. Baseline safety variables

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

9. COMPLIANCE

For patients using Healsea® Children, compliance will be calculated according to the following formula and analysed on the FAS:

Compliance (%) = Real number of uses × 100 / 20

With:

- Real number of uses = total number of uses of the treatment from D1 to D10

The number of uses at each day is computed as follows:

- If the patient answered “No” to the question “Did patient use Healsea today?” or “Yes” to the question “Have you not taken Healsea Children today?” then 0;
- If the patient answered “Yes” to the question “Did patient use Healsea today?” then:
    - If the patient answered “Yes” to the question “Did patient use Healsea once a day?” then 1;
    - If the patient answered “Yes” to the question “Did patient use Healsea more than twice a day?” then 3;
    - If he/she did not answer “Yes” neither to the question “Did patient use Healsea once a day?” nor to the question “Did patient use Healsea more than twice a day?” nor to the question “Have you not taken Healsea Children today?” then 2.

Compliance will be described only on Healsea® Children arm.

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) between the means AUC of WURSS-K score during first ten days of symptoms in each group.

The answers of the fourteen first items of the WURSS-K questionnaire are scored **from 0 to 3** (0: negative answer; from 1 to 3: positive answer with an increasing severity level). See the daily symptom report in appendix (§13.3).
The total WURSS-K score at each time point is the sum of the scores of the fourteen first items of the WURSS-K questionnaire:

$$\text{At each time point t: } \mathbf{WURSS_{TOT}(t)} = \sum_{j \text{ in } \{1;\ ...;\ 14\}} \mathbf{WURSS_j(t)}$$

AUC of WURSS-K score will be computed by the method described in §6.4.6.

Subjects will be analysed on the Full Analysis Set and the Per-Protocol Set.

10.2. Analysis of the secondary efficacy criteria

The analysis of the secondary endpoints will involve multivariate analysis.

The selection of variables in multivariate analysis will be performed using a 0.20 significance level and a stepwise method. Whole the multivariate analyses specified below involve the treatment and, in order to adjust for confounding, all the potential confounding factors as explanatory variables:

- Temperature at baseline (°C);
- Symptoms' scores at baseline.

10.2.1. Modelling of AUC on total WURSS by multivariate ANCOVA

The analysis of the impact of the treatment chosen on the primary endpoint will be enriched by means of a multivariate ANCOVA model with the AUC of the WURSS-K during first ten days of symptoms as dependent variable. Subjects will be analysed on the Full Analysis Set and the Per-Protocol Set.

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

Hereinafter, the "recovery date" is the first day of two last days the patient answered to the WURSS-K 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 7 of WURSS-K 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 last observation carried forward (LOCF).

The considered symptomatic days are between D1 and either D30, 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 7 of the WURSS-K 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 D30 or at the end of the study, and the censoring date will be the date of D30 or the reference end date, whichever occurs first.

For patients who never reported the presence of a given symptom (never ticked "a little bad", "bad" or "very bad"), if they completed the questionnaire at D1, then their origin date will be D1, they will be censored at D1 and their corresponding duration will be zero, else they will have neither origin date nor censoring date and the corresponding duration will be missing.

For each of the items 2 to 7 of the WURSS-K questionnaire, the impact of the treatment chosen on the corresponding cold symptom' duration will be analysed by means of a Cox model. Subjects will be analysed on the FAS.

10.2.3. Impact of the treatment chosen on the risk to develop respiratory complication requiring antibiotics prescription

The impact of the treatment chosen on the risk to develop respiratory complication requiring antibiotic prescription during a 20-day follow-up period will be analysed by a multivariate logistic model. Subjects will be analysed on the FAS.

10.2.4. Impact of the treatment chosen on the intake of a conventional cold medication

The impact of the treatment chosen on the intake of a conventional common cold medication will be analysed on the FAS.
Common cold medications are antibiotics, antipyretics, mucolytics, decongestants, antitussives, systemic and topical corticosteroids.

The use/non-use of these medications (if the patient used it at least one day from D1 to D30, or if he/she never used it) will be modelled by a multivariate logistic regression.

The number of days of intakes 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 D30.

The number of days of intakes of these medications will be modelled by a multivariate Poisson regression.

The same analyses will be performed for each category of medications: antibiotics, antipyretics, mucolytics, decongestants, antitussives, systemic and topical corticosteroids.

10.2.5. Impact of the treatment chosen on the number of family members in close contact developing common cold symptoms

The impact of the treatment chosen on the number of family members in close contact developing common cold symptoms after the patient all over the study period will be analysed by means of a multivariate Poisson regression. Subjects will be analysed on the FAS.

10.3. Concomitant treatments

Concomitant treatments are coded using the WHO-DRUG dictionary version 2021 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 20.1. 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 FAS.

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

- it was reported at least one day after screening, or at least two days after screening in the case of the AE "rhinitis";
- 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 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 will be listed if applicable.

11. SAFETY

The following analyses will be performed on the FAS.

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 FAS.

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 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 and Preferred term.

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 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.

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-K 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 D30 or at the end of the study, whichever occurs first.

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Table	14.2.4.1.1	Summary of non-related adverse events – Full Analysis Set
Table	14.2.4.1.2	Non-related treatment-emergent adverse events by System Organ Class and Preferred Term – Full Analysis Set
Listing	14.2.4.2.1	Listing of non-related adverse events leading to definitive discontinuation of the trial device – Full Analysis Set (if applicable)
SAFETY – INCIDENTS		
Table	14.3.1.1	Summary of incidents– Full Analysis Set
Table	14.3.1.2	Related treatment-emergent adverse events by System Organ Class and Preferred Term – Full Analysis Set
Listing	14.3.2.1	Listing of serious incidents – Full Analysis Set (if applicable)
Listing	14.3.2.2	Listing of incidents leading to definitive discontinuation of the trial device – Full Analysis 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
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

Type	Number	Title
Listing	16.2.5.2	Daily administration of Healsea Children
Listing	16.2.6.1	Questionnaire WURSS-K
Listing	16.2.6.2	Previous and concomitant medications by subject
Listing	16.2.6.3	Contaminations of relatives
Listing	16.2.7.1	Adverse events, incidents and expected side effects

13.2. Mock tables

Table 14.1.1.1. Subjects' disposition – Screened subjects

	Healsea Children N=XX	Conventional therapy 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%)
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 Exclusion		No Yes

Figure 14.1.1.1. Subjects' disposition – Screened subjects

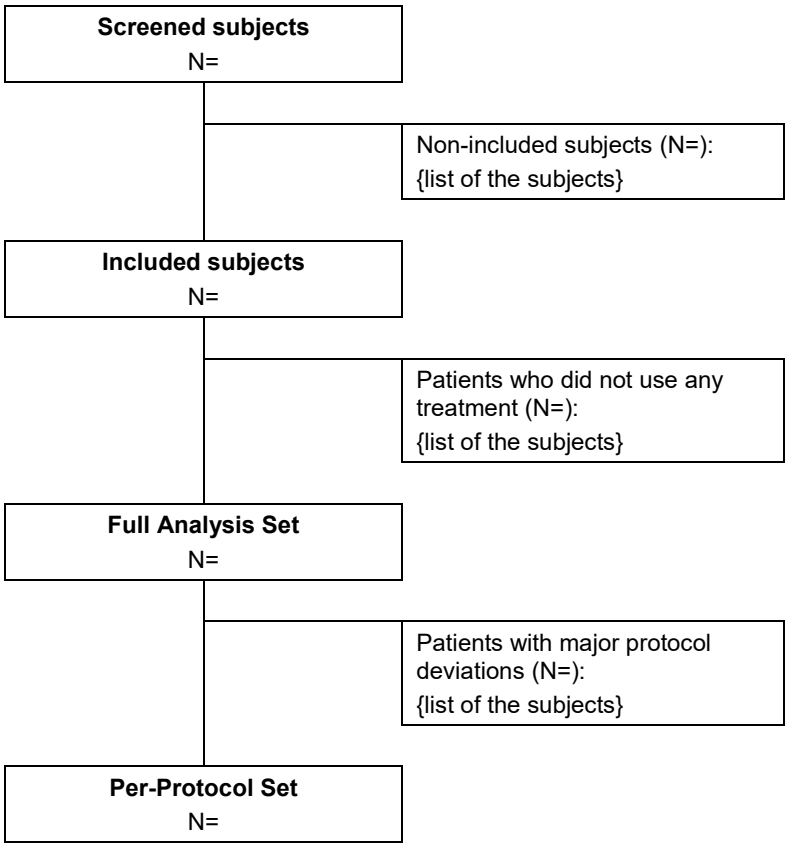

Table 14.1.1.2.1. Summary of protocol deviations – Included subjects

	Healsea Children N=XX	Conventional therapy N=XX	Total N=XX
Category of deviation			
Minor	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Major	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	Full Analysis Set	Per-Protocol Set	Protocol deviation	Classification of deviation

Table 14.1.1.2.2. Premature withdrawal – Reason of withdrawal

	Healsea Children N=XX	Conventional therapy 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	Full Analysis Set	Per-Protocol Set	Reason of withdrawal

Table 14.1.2.1. Demographic characteristics – Full Analysis Set

	Healsea Children N=XX	Conventional therapy 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 – Full Analysis Set

ATC1 - ATC2	Healsea Children N=XX	Conventional therapy 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 – Full Analysis Set

SOC - Preferred Term	Healsea Children N=XX	Conventional therapy 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 – Full Analysis Set

	Healsea Children N=XX	Conventional therapy N=XX	Total N=XX
Temperature (°C)			
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)		
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 14.1.3. Summary of compliance on Healsea Children arm – Full Analysis Set

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

Table 14.1.4. Study duration by subject – Full Analysis Set

	Healsea Children N=XX	Conventional therapy 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. Global AUC on total WURSS per treatment group – Per-Protocol Set

	Healsea Children N=XX	Conventional therapy N=XX	Total N=XX
Global AUC on total WURSS			
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. Modelling of AUC on total WURSS by multivariate ANCOVA – Per-Protocol Set

	Healsea Children N=XX	Conventional therapy N=XX
Global AUC on total WURSS		
ANCOVA model :		
AUC = Treatment + …		
Type 3 Tests of Fixed Effects		
Treatment	XXX	
…	XXX	
Adjusted mean		
LSMeans (SE)	XX.X (XX.X)	XX.X (XX.X)
[LSM 95%CI]	[XX.X; XX.X]	[XX.X; XX.X]
Adjusted mean (diff. vs Conventional therapy)		
LSMeans (SE)	XX.X (XX.X)	
[LSM 95%CI]	[XX.X; XX.X]	
Contrast vs Conventional therapy, p=	XXX	

Table 14.2.2.2. Impact of the treatment chosen on the cold symptoms' duration – Full Analysis Set

	Healsea Children N=XX	**Conventional therapy N=XX**
XXX – Duration (days)		
N	XX	XX
Missing	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Median	XX	XX
Q1/Q3	XX / XX	XX / XX
Min/Max	XX / XX	XX / XX
Hazard Ratio [95%CI]	XX.X [XX.X; XX.X]	
p-value (Wald)	XXX	

Table 14.2.2.3. Impact of the treatment chosen on the risk to develop respiratory complication requiring antibiotic prescription during a 20-day follow-up period – Full Analysis Set

	Healsea Children N=XX	**Conventional therapy N=XX**
Use of antibiotics during 20-day follow-up period		
N	XX	XX
Missing	XX	XX
No	XX.X (XX.X%)	XX.X (XX.X%)
Yes	XX.X (XX.X%)	XX.X (XX.X%)
Logistic model :		
Odds Ratios [95%CI]		
Treatment	XX.X [XX.X; XX.X]	
…	XX.X [XX.X; XX.X]	
p-values (Wald)		
Treatment	XXX	
…	XXX	

Table 14.2.2.4.X. Impact of the treatment chosen on the intake of XXX – Full Analysis Set

	Healsea Children N=XX	Conventional therapy 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%)
Poisson regression :		
Type 3 Tests of Fixed Effects		
Treatment	XXX	
…	XXX	
Use of XXX		
N	XX	XX
Missing	XX	XX
No	XX.X (XX.X%)	XX.X (XX.X%)
Yes	XX.X (XX.X%)	XX.X (XX.X%)
Logistic model :		
Odds Ratios [95%CI]		
Treatment	XX.X [XX.X; XX.X]	
…	XX.X [XX.X; XX.X]	
p-values (Wald)		
Treatment	XXX	
…	XXX	

Table 14.2.2.5. Impact of the treatment chosen on the number of family members in close contact developing common cold symptoms after the patient all over the study period – Full Analysis Set

	Healsea Children N=XX	Conventional therapy N=XX
Number of family members in close contact developing common cold symptoms after the patient all over the study period		
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%)
Poisson regression :		
Type 3 Tests of Fixed Effects		
Treatment	XXX	
…	XXX	

Table 14.2.3. Concomitant treatments – Full Analysis Set

ATC1 - ATC2	Healsea Children N=XX	Conventional therapy 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 – Full Analysis Set

	Healsea Children N=XX		Conventional therapy 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
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 – Full Analysis Set

SOC - Preferred Term	Healsea Children N=XX		Conventional therapy 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 – Full Analysis 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– Full Analysis Set

	Healsea Children N=XX		Conventional therapy 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
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 – Full Analysis Set

	Healsea Children N=XX		Conventional therapy 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 – Full Analysis 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-K questionnaire – Daily symptom report

Wisconsin Upper Respiratory Symptom Survey for kids—daily symptom report

Day:	Date:	Time:	ID:

Please fill in one circle for each question:

	Not sick	A little sick	Sick	Very sick
How sick do you feel today?	O	O	O	O

How bad are your cold symptoms? (Overall, since yesterday)

	Do not have this	A little bad	Bad	Very bad
Runny nose	O	O	O	O
Stuffy nose	O	O	O	O
Sneezing	O	O	O	O
Sore throat (hurts to swallow)	O	O	O	O
Cough	O	O	O	O
Feeling tired	O	O	O	O

Since yesterday, how **hard** has it been to:

	Not at all	A little hard	Hard	Very hard
Think	O	O	O	O
Sleep	O	O	O	O
Breathe	O	O	O	O
Talk	O	O	O	O
Walk, climb stairs, exercise	O	O	O	O
Go to school	O	O	O	O
Play with friends	O	O	O	O

Compared to yesterday, I feel my cold is...

A lot better	A little better	The same	A little worse	A lot worse
O	O	O	O	O

I completed this page: ☐ all by myself ☐ with some help ☐ with a lot of help

Who helped you? _____

Figure 2 – Wisconsin Upper Respiratory Symptom Survey for Kids (WURSS-K) – Daily symptom report