

BI Study Number:	1368-0121
Title:	NON-INTERVENTIONAL STUDY OF PATIENTS WITH NETHERTON SYNDROME TO CHARACTERISE NATURAL HISTORY OF THE DISEASE
NCT number:	NCT05902663
Date:	March 21, 2024

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Document Number:	<Document number from Document Management System (DMS) for submission documents, if relevant>
BI Study Number:	1368-0121
BI Investigational Product(s)	-
Title:	Non-interventional study of patients with Netherton Syndrome to characterise natural history of the disease
Brief lay title:	Natural History of Netherton Syndrome
SEAP version identifier:	Version 1.0
Date of last version of SEAP:	N/A
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1. LIST OF ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
CDLQI	Children's Dermatology Life Quality Index
CI	Confidence Interval
ClinRO	Clinician-Reported Outcomes
COA	Clinical Outcome Assessment
CoE	Centre of Excellence
DLQI	Dermatology Life Quality Index
eCRF	Electronic Case Report Form
ED	Emergency Department
FDLQI	Family Dermatology Life Quality Index
FLACC	Face, Legs, Activity, Cry, Consolability scale
FPS-R	Face Pain Scale- Revised
HADS	Hospital Anxiety and Depression Scale
HCRU	Healthcare Resource Utilisation
HRQoL	Health-Related Quality of Life
IASI	Ichthyosis Area Severity Index
IASI-E	Ichthyosis Area Severity Index – Erythema
IASI-S	Ichthyosis Area Severity Index – Scaling
ICF	Informed Consent Form
ICU	Intensive Care Unit
IGA	Investigator Global Assessment
IgE	Immunoglobulin E
ILC	Ichthyosis Linearis Circumflexa
IQR	Interquartile range
MOS	Medical Outcomes Study
N	Non missing values
N/A	Not Applicable
NASA	Netherton Area Severity Assessment Score
NRS	Numeric Rating Scale

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NS	Netherton Syndrome
ONIS	Observational and Non-interventional study
PGI-S	Patient Global Impression of Severity
PIQ-C	Paediatric Itch Questionnaire - Child
PRO	Patient-Reported Outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred Term
QoL	Quality of Life
RWE	Real World Evidence
SD	Standard Deviation
SE	Scaly Erythroderma
SEAP	Statistical and Epidemiological Analysis Plan
SHA	Scalp Hair Assessment
SOPs	Standard Operating Procedures
SPINK5	Serine Protease Inhibitor of Kazal Type 5
TI	Trichorrhexis Invaginata
TM Epi	Team Member Epidemiology
UK	United Kingdom
VAS	Visual Analogue Scale
WPAI-SHP	Work Productivity and Activity Impairment – Specific Health Problem

2. RESPONSIBLE PARTIES

Observational and Non-Interventional Study (ONIS) Statistician [Statistical and epidemiological analysis plan (SEAP) author]

SEAP reviewers are:

- Boehringer Ingelheim (BI) ONIS Lead [SEAP reviewer] (in all cases): [REDACTED]
- ONIS Data Manager [SEAP reviewer] (in all cases): [REDACTED]
- RWE Centre of Excellence (CoE) [SEAP reviewer] (for all globally initiated studies and for local studies) involving BI products and Global ONIS not involving BI products: [REDACTED]
- PSTATs: [REDACTED] and [REDACTED]
- TM Epi [SEAP reviewer] (When BI ONIS Lead is not TM Epi; in all cases): BI ONIS Lead

- Global Medical Advisor: [REDACTED]
- TM HEOR: [REDACTED]

3. PURPOSE AND SCOPE

The purpose of this Statistical and Epidemiological Analysis Plan (SEAP) is to provide a detailed description of the statistical analyses that will be performed for studying Natural history of Netherton Syndrome. Analyses described in this SEAP are based on protocol Version 2.0; dated: 28 November 2023.

4. AMENDMENTS AND UPDATES

N/A. This is the original SEAP v 1.0.

5. RESEARCH QUESTION AND OBJECTIVE

The goal of this observational and non-interventional study (NIS) is to collect real-world data to describe natural history of Netherton Syndrome (NS).

The NIS will (1) leverage abstraction of information from existing medical records and (2) conduct new primary data collection on clinician- and patient-reported outcome assessments to achieve the following objectives:

Primary objective:

- To assess severity of NS by the Ichthyosis Area Severity Index (IASI).

Secondary objective:

- To assess severity of NS by the Investigator Global Assessment (IGA).

Further objectives:

- To describe the socio-demographics and clinical characteristics of patients diagnosed with NS.
- To describe the treatment patterns in patients with NS.
- To describe the healthcare resource utilisation (HCRU) in patients with NS.
- To characterise episodes of flares of NS and frequency of occurrence.
- To describe the severity of manifestations and Health-Related Quality of Life (HRQoL) including pain, itch, mental health, sleep, hair assessment, disease burden on family and loss of work and productivity.

6. RESEARCH METHODS

6.1 STUDY DESIGN

This is an observational and non-interventional, multi-centre cohort study to be conducted in multiple countries to collect real-world data on patients managed for NS in routine clinical practice. The study will enrol approximately 100 patients across the entire study. To achieve the study objectives of collecting data to describe the natural history of NS and to assess longitudinal assessment of clinical outcomes, a two-part study is proposed:

- [Part 1] inclusion of patients diagnosed with NS (including deceased patients and patients whose survival status are not known) to collect existing data in medical records.
- [Part 2] inclusion of patients who are not participating in any clinical trial to collect new data on clinical outcome assessments at enrolment, within 2 weeks of enrolment, and at approximately 16 and 52 weeks. Clinical data will continue to be abstracted from patient's charts during the 52-week follow-up.

Informed consent/assent will be obtained, if required by local and country regulations, for study participation in Part 1 and Part 2. Patients will have the choice to enrol in either Part 1 only or both Parts 1 and 2.

6.2 SETTING

This study will be conducted in hospitals/clinical centres where patients with NS are typically managed in real-world clinical practice. The study will include study sites across several countries in North America, Europe, and Asia.

For practical reasons, site selection will prioritize centres where a higher number of patients can be enrolled to achieve the target study sample size. Approximately 22 centres will participate in this study; more sites may be included to achieve the target study sample size.

6.3 STUDY POPULATION

Sites will identify all patients diagnosed and treated for NS in routine clinical practice to form the base cohort for study eligibility assessment. Patients in the base cohort will be further reviewed for study eligibility based on the inclusion and exclusion criteria.

6.3.1 Part 1 Population

The Part 1 population is defined as all patients who fulfil all I/E criteria for Part 1 and who participate in only Part 1 of the study.

6.3.2 Part 1 + Part 2 Population

This population is defined as all patients who fulfil all I/E criteria and participate in Part 1 and in Part 2 of the study. Participation in Part 2 is fulfilled if enrolment and at least one PRO or ClinRO is completed at Week 2, Week 16, or Week 52.

6.4 STUDY VISITS

For Part 1 of the study, data will be collected solely from existing medical records. Patients who participate in Part 2 of the study will be evaluated using the ClinRO and PRO assessments:

- at the time of study enrolment,
- within 2 weeks of enrolment assessment (for test-retest evaluation),
- at approximately 16 weeks (± 2 weeks), and
- at the end of the 52-week study follow up (± 4 weeks).

At all time-points of ClinRO and PRO assessments, patients will be reimbursed for their travel expenses and be compensated for their time spent on completing the assessments if permitted by local regulations.

7. VARIABLES

Data collection will include variables as assessed, measured and documented in patients' medical records as permitted by local routine clinical care. Table 1 summarises the study variables by category of study outcomes.

Table 1 Study Variables*

Cohort characterisation/ Study outcomes	Variables
Socio-demographics	• Age • Sex • Race (where allowed/recorded) • Ethnicity (where allowed/recorded) • Marital status • Education level • Employment status • Consanguinity (i.e., parents first cousins) • Family history of NS • Residential location of patient at time of diagnosis (urban/rural)
Diagnosis of Netherton Syndrome (First clinical signs, initial diagnosis and changes over time)	• Skin colour classification (Fitzpatrick scale) • First clinical signs or symptoms ○ Diagnostic method(s) ○ Date of initial onset of signs and symptoms ○ Possible diagnosis ○ Treatments for possible diagnosis • Date of referral to the site • Initial diagnosis of NS ○ Date or year or age at initial diagnosis ○ Diagnostic method(s) ○ Genetic test (date, specify SPINK5 mutation) ○ Skin biopsy (date), LETKI protein absent or reduced level ○ Clinical diagnosis (ILC, TI) • Phenotype at initial diagnosis and subsequent clinical follow-up assessments • Severity of erythroderma • Severity of erythema • Severity of scaling • Severity of skin thickening • Severity of elevated red bumps on the skin • Number of defined lesions • Worst Itch (- none, mild, moderate, severe, no information in charts) • Worst Pain (e.g., - none, mild, moderate, severe, no information in charts) • Hair assessment (e.g., date of hair microscopy, severity of hair loss, TI assessment)
Longitudinal assessment of NS signs/symptoms (worst severity)	• Scaly erythroderma • Ichthyosis Linearis Circumflexa (ILC) • Itch • Pain • Skin infections

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Cohort characterisation/ Study outcomes	Variables
Vital signs and anthropometrics (Initial diagnosis and change over time)	• Height • Weight • Blood pressure (SBP and DBP) • Temperature • Respiratory rate • Pulse oximetry • Pulse rate • Vital status (i.e., information to be collected at study enrolment and during 52-week follow-up; date of study discontinuation if prior to week 52, date of death if known or date last known to be alive)
Gestational information	• Preterm birth (yes/no) • Gestational age • Birth weight • Birth length • Presence of colloidal membrane at birth • Ability to be breastfeed • Neonatal allergy to cow's milk (yes/no) • Age when Failure to thrive (weight for length <5th percentile or length <5th percentile) detected • Complication during delivery
Dietary history	• Feeding (date of initiation and duration) ○ Oral ○ Tube feeding ○ Gastrostomy ○ Parenteral ○ Parenteral and gastrostomy
Lifestyle habits	• Substance use ○ Type (tobacco, nicotine, vaping, alcohol, caffeine, cannabis) ○ Status (never, current, former) ○ Duration of use

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Cohort characterisation/ Study outcomes	Variables
Co-morbidities and NS-related complications with associated treatments and healthcare resource utilization (if applicable)	• Allergies and intolerance • Asthma • Atopic eczema • Cardiovascular • Covid (date of infection, vaccination status) • Developmental delay type (e.g., cognitive, language, other) • Encephalitis • Gastrointestinal disorder requiring medication or intervention and/or healthcare resource utilization (e.g., chronic diarrhoea, recurrent vomiting, gastro-oesophageal reflux, constipation, irritable bowel syndrome) • Growth hormone deficiency • Hyperactivity • Hyper-IgE syndrome (i.e., IgE > 22.8 kU L-1) • Hypereosinophilia • Hyponatraemia (i.e., Na⁺ >145 mmol L-1) • Hypothyroidism • Infections, type (e.g., viral, bacterial, fungal), location of infection and specify organism (if applicable and available) • Skin cancer • Other malignancies • Malnutrition • Pruritus
Drug and Non-Drug Treatments for NS/ comorbidities/ complications	• Treatment (type,* generic name, dose provided, frequency, start and stop date, route of administration, reason for discontinuation) • Indication • Any clinical trial participation (as a treatment sequence, collect information on date of informed consent and name of investigative agent, as available in the medical chart)
Flare	• Date of occurrence • Outcome of flare • Symptoms (exacerbation of prior symptom or new symptom) • Treatment given (including medication, visits to ED, ICU/hospital admission) • Potential source(s) of flare • Severity of erythroderma, scaling, skin infection, pain, itch
Health resource utilisation (All cause and NS-related as primary reason)	• Outpatients visit (date, reason) • ED visit (date, reason) • Hospital admission (date of admission, date of discharge, reason) • ICU admission (date of admission, date of discharge, date of death and reason)
Clinical outcome assessments Clinician-reported**	• Ichthyosis Area Severity Index (IASI) (All age groups) • Investigator Global Assessment (IGA) (All age groups) • Netherton Area Severity Assessment (NASA) (All age groups) • Face, Legs, Activity, Cry, Consolability (FLACC) scale (≤ 2 years)

Cohort characterisation/ Study outcomes	Variables
Patient-reported outcomes Patient-reported**	• Itch assessment using age-appropriate tools: ○ Itch Numeric Rating Scale (NRS) (≥12 years) ○ 5-D Itch Scale (≥8 years) ○ PROMIS Pediatric Short Form v1.0 – Itch 6a (PIQ-C) (8–11 years) ○ PROMIS Parent Report/Proxy Short Form v1.0 - Itch 6a (PIQ-C) (1–7 years) • Pain assessment using age-appropriate tools: ○ Pain Numeric Rating Scale (NRS) (≥12 years) ○ Face Pain Scale – Revised (FPS-R) (3–11 years) • Quality of life assessment using age-appropriate tools: ○ Dermatology Quality of Life Index (DLQI) (≥16 years) ○ Children’s Dermatology Life Quality Index (CDLQI) (4–15 years) ○ Family Dermatology Life Quality Index (FDLQI) (to be completed by a family member who is ≥16 years) • Patient Global Impression of Severity (PGI-S) for erythema (≥12 years) • PGI-S for scaling (≥12 years) • Scalp Hair Assessment Patient Reported Outcome™ (SHA PRO™) (≥15 years, but due to the simplicity of the question it will be administered in ≥12 year of age group) • Hospital Anxiety and Depression Scale (HADS) (≥12 years) • Sleep disturbance assessment using age-appropriate tools: ○ Medical Outcomes Study (MOS) Sleep Scale (≥18 years) ○ PROMIS Pediatric Short Form – Sleep Disturbance 4a (8 - 17 years) ○ PROMIS Parent Report/Proxy Short Form – Sleep Disturbance 4a (1–7 years) • Work Productivity and Activity Impairment-Specific Health Problem (WPAI-SHP) (≥16 years) • Adult caregiver WPAI-SHP (≥16 years)
* Treatment may be any therapy use over-the-counter or prescribed as per real-world clinical standard including treatment received through a compassionate use program. Information on investigational treatment will be abstracted for Part 1. Patients who become participants of any investigational trial during Part 2 participation will be early terminated for the NIS; information on date consent and name of investigational treatment (if known) will be documented as part of description of treatment patterns in this NIS. **Data availability will vary across sites. Age ranges specified in parentheses for the COA tools reflect the specific age groups where the COAs have been administered for other related contexts of use and will be administered to the age groups in this study.	

7.1 EXPOSURES

This is a natural history of disease study. As part of the study objectives, treatment patterns (including medications, procedures, health care use) in patients will be described, but there is no evaluation of a specific exposure.

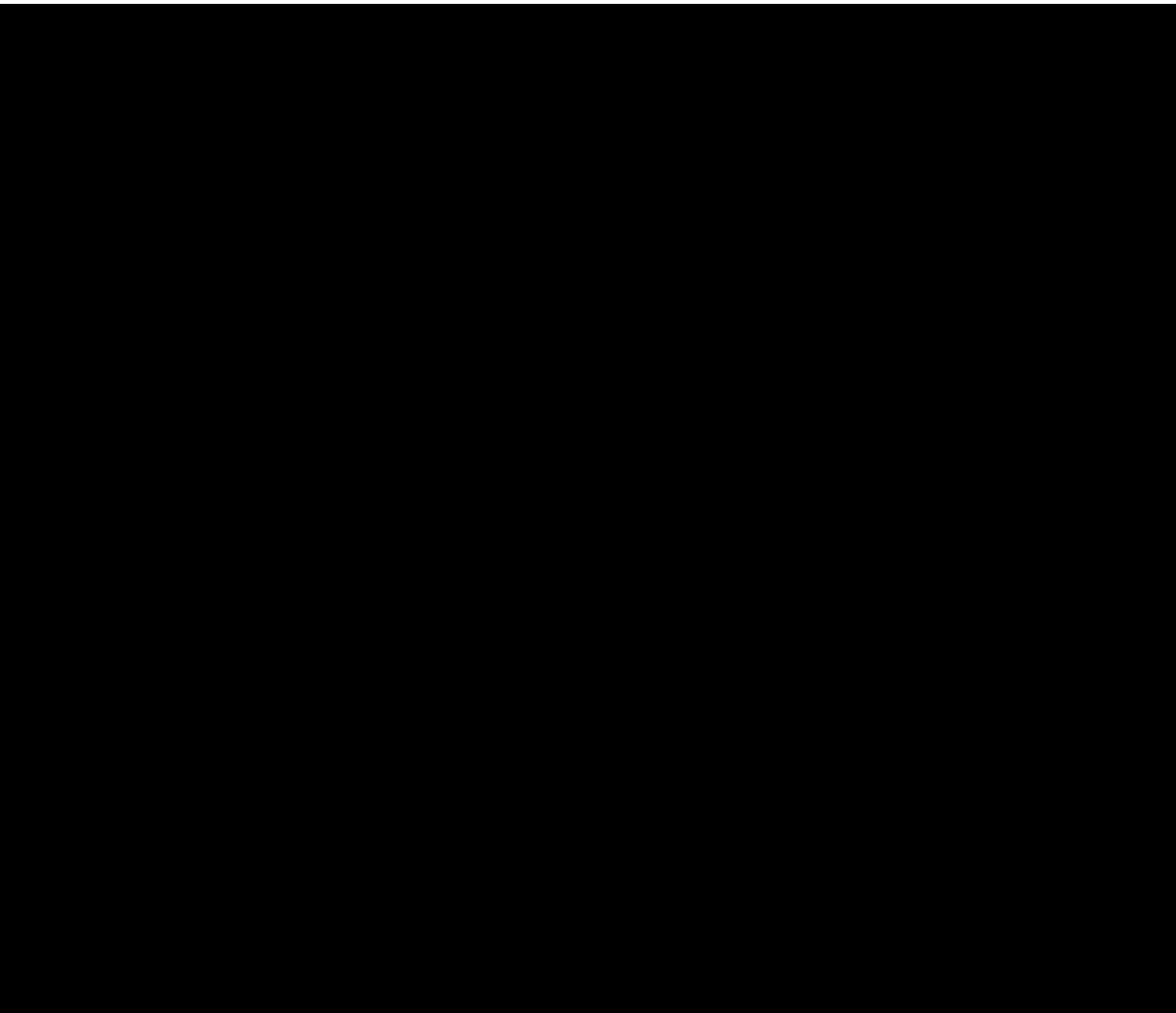
7.2 OUTCOMES

7.2.1 Primary outcomes

IASI is a ClinRO that results in a composite score comprising severity of erythema and scaling in different body regions as a function of their respective body surface areas. Severity of erythema and scaling is rated on a 5-point Likert scale of 0–4 in each of 4 body regions: head and neck (including scalp), arms (including palms), legs (including soles) and trunk, prorated based on body surface area in these body regions and the percentage of involvement in each of these body regions. The total IASI score ranges between 0–48 (i.e., sum of a maximum score of 24 for erythema and maximum score of 24 for scaling). Higher score denotes worse clinical severity.

7.2.2 Secondary outcomes

IGA is a ClinRO that will assess the global severity of erythema and scaling in NS patients using a 5-point Likert scale ranging from 0=clear, to 4=severe.



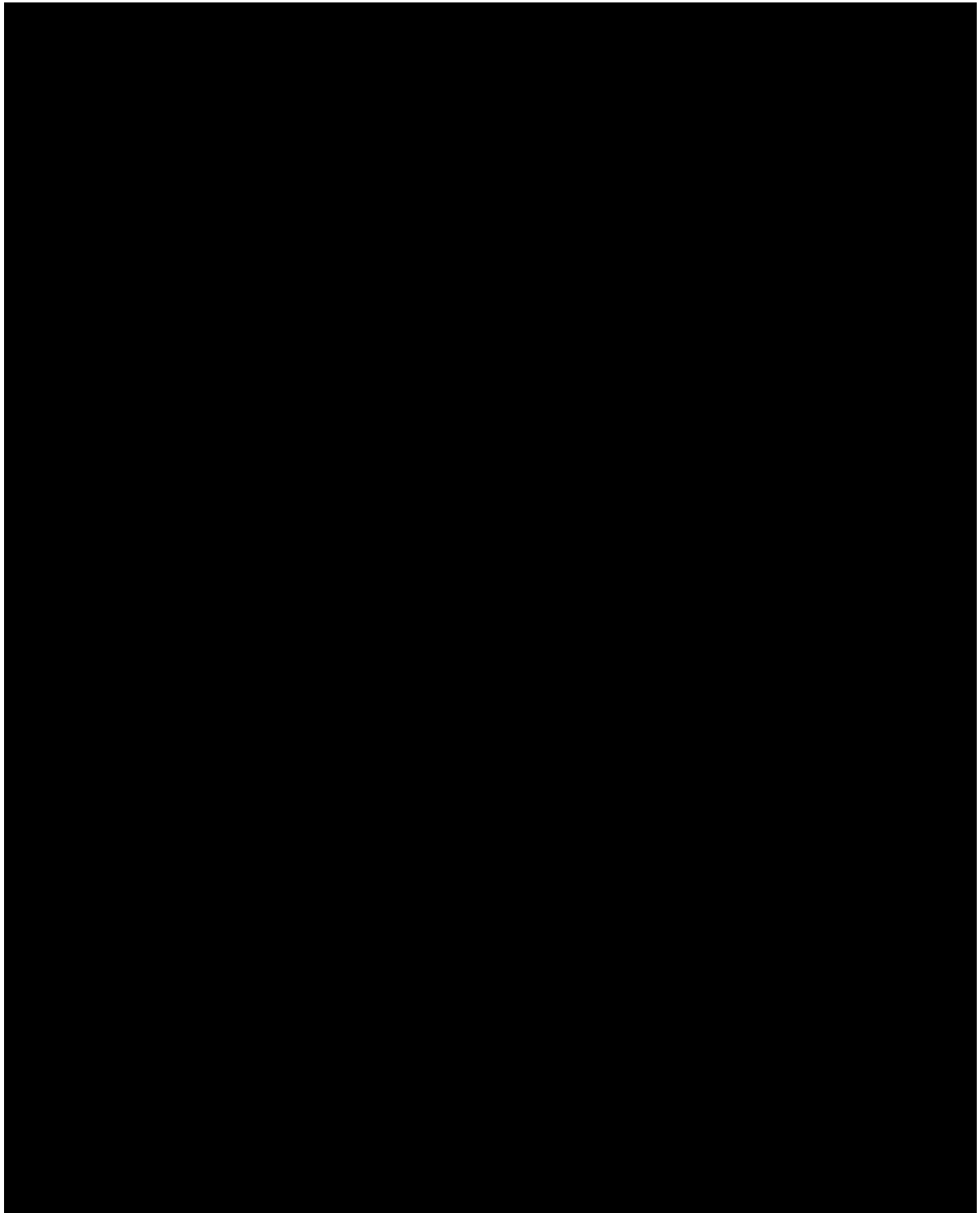
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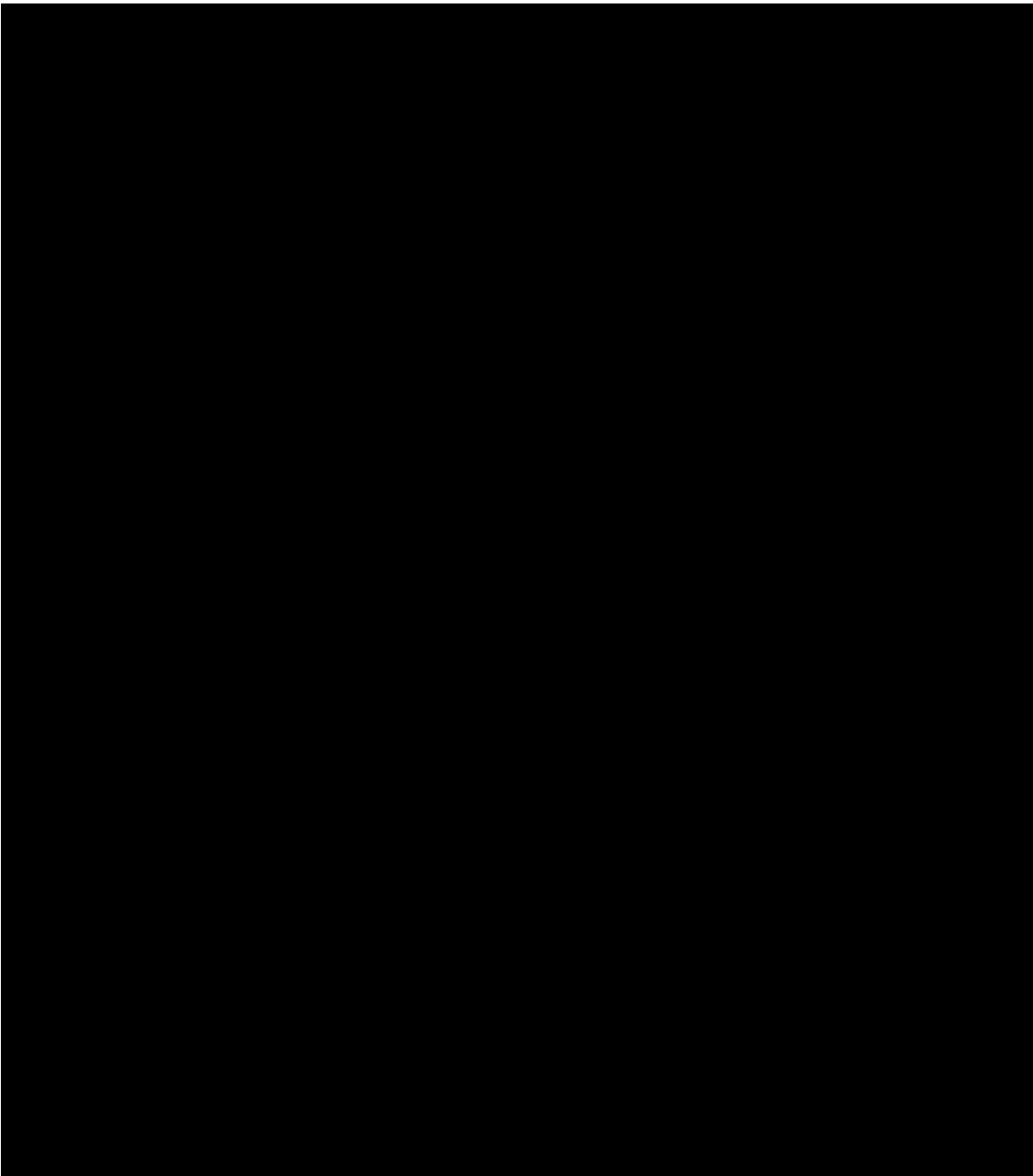
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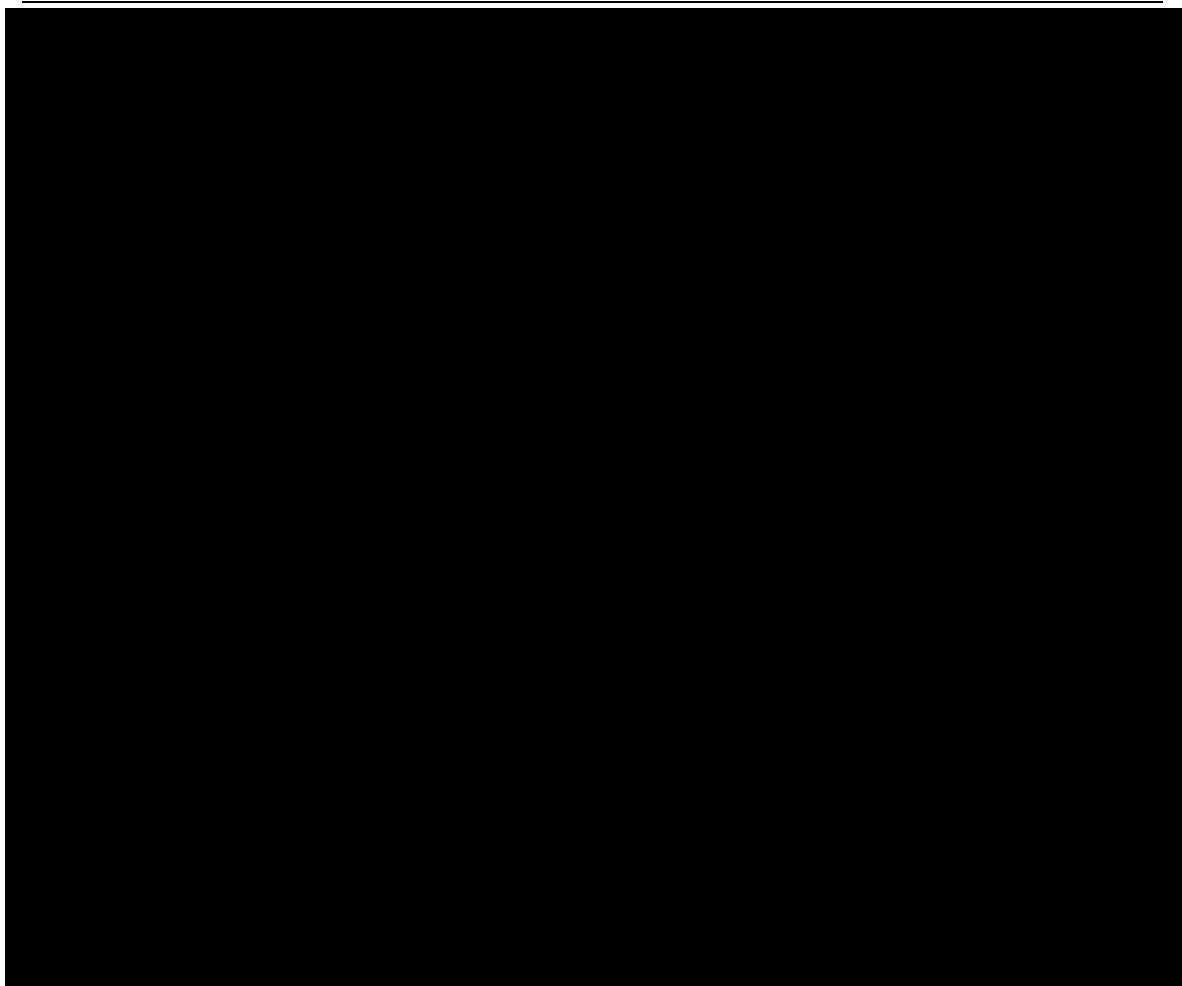
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7.3 COVARIATES

Possible covariates for the explorative analysis of potential predictors of ClinRO and PRO variables as well as for the identification of possible risk factors for NS flares are the socio-demographic, clinical and treatment variables.

8. DATA SOURCES

The two main data sources of this NIS are (1) existing medical records and (2) new, primary data collected from clinicians and patients.

9. DATA MANAGEMENT AND SOFTWARE / TOOLS

9.1 SOFTWARE/TOOLS

All analysis will be performed using SAS software, Version 9.4 or a later version.

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9.2 HANDLING OF MISSING VALUES

There are no plans for imputing missing values other than imputing partial missing date values or partial date values where only month and year or only year is captured.

The following algorithm should be used for the imputation of partially missing date of diagnosis of NS:

- If month and year are available, impute the first day of the months as missing day
- If year is available and day and month is missing, impute 01Jan as day and month.
- If date of diagnosis is completely missing, impute 01Jun of the birth year (if available)

The following algorithm should be used for imputing partially missing date values for the date of death and date last known to be alive:

- If month and year are available, impute the last day of the month
- If only year is available, impute 31 Dec as missing day and month.
- If year is missing, regardless of whether or not day or month is available, do not impute any partial missing date value.

The following algorithm should be used for imputing partially missing date values for date of the initial onset of signs and symptoms and partial dates for the assessment of vital signs:

- If month and year are available, impute the first day of the months as missing day
- If year is available and day and month is missing, impute 01Jan as day and month.

The following algorithm should be used for imputing partially missing date values for date of diagnosed condition (First Clinical Signs/Symptoms of Netherton Syndrome page), date failure to thrive was observed or diagnosed (Gestational Information page), diagnosis of Co-Morbidities/Netherton Syndrome Complications, for hair assessments, date of assessment of phenotype, and onset date of flares, specialists and ED visits and hospital and ICU admission dates (HCRU page), and start dates of medical therapies and procedures:

- If month and year are available, impute the first day of the months as missing day
- If year is available and day and month is missing, impute 01Jan as day and month.
- If the imputed date value is prior to the date of the first signs and symptoms, impute the date of the first signs and symptoms.

The following algorithm should be used for imputing partially missing date values for date of initiation of assisting of feeding:

- If month and year are available, impute the first day of the months as missing day
- If year is available and day and month is missing, impute 01Jan as day and month.
- If the imputed date value is prior to the date of the diagnosis date for failure to thrive, impute the date of the diagnosis for failure to thrive.

The following algorithm should be used for imputing partially missing date values for date of the end date of assisting of feeding, resolution date of flairs, discharge dated from hospital and ICU (HCRU page), end dates for medical therapies and procedures:

- If month and year are available, impute the last day of the months as missing day

- If year is available and day and month is missing, impute 31Dec as day and month.
- If the imputed date is after the date last known to be alive or date of death or the enrolment date (Patients participating in Part 1) or Week 52 visit date, impute date last known to be alive, date of death, enrolment date, or the week 52 visit date, respectively.

Partial missing date values for the ClinROs and PROs will be substituted by the visit dates of enrolment, week 2, week 16, and week 52, respectively. No imputation of partial missing date values will be applied here.

The following date values will be only presented in data listings and partial missing date values will not be imputed:

- Initial diagnosis of Netherton Syndrome page: Date of test, date of skin biopsy, date of clinical examination
- Clinical Outcome Assessments: date of evaluation

All imputed date values will be flagged in the analysis dataset. Date imputations will be applied prior to the process of assigning study day and the calculation of any time frames and should be retained in the analysis datasets, but the data listings should display the original, partially missing dates.

9.3 HANDLING OF INCONSISTENCIES IN DATA AND OUTLIERS

To avoid conflicting values in calculated ages, all age calculations will be based on the age at enrolment. The year of birth will not be used in the statistical analysis for any calculations. Imputation of partial missing date values are constructed to avoid conflicting data values as much as possible. Imputation rules will be reviewed and updated in case conflicting date values will occur from imputations of multiple partial missing date values. Generally, all possible conflicting values which are not resolved by Data Management will be discussed with the study team and will be handled on a case-by case basis.

10. DATA ANALYSIS

General Analysis Considerations:

Summary statistics for continuous variables include the number of non-missing values (n) mean, standard deviation (SD), minimum (min), Q1, median, Q3, and maximum (Max). Summary statistics for categorical data included the counts (n) and percentages for each category. Confidence intervals for dichotomous variables will be calculated by the method of Clopper-Pearson.

Frequency tables and other descriptive summary statistics, like incidence rates will be calculated if there are at least 2 patients with the condition/events. If there are less than 2 patients/events, these patient characteristics or events will only be included in data listings but not summarized.

Assignment of Study Days

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For the purposes of data listings and summaries, “Study Day” will be calculated relative to enrolment (i.e., date of interest – date of first dose of enrolment). One day will be added if this difference is ≥ 0 , so that the enrolment date is considered “Study Day 1.” The day prior to enrolment is considered “Study Day -1”. For analysis purposes, there will be no “Study Day 0”. With this approach, patients enrolled in Part 1 will have only negative study days, for patients enrolled in Part 1 + Part 2, the retrospective part will have negative study days, the prospective part positive study days.

Baseline Determination and Assignment of Study Visits

Protocol-defined assessments will be “slotted” to study visits based on collection date and applying the rules summarized in the following table.

Visit	Enrolment/Baseline	Week 2 Assessment	Week 16 Assessment	Week 52 Assessment
Target Study Day	1	15	113	365
Study Day Range	1	2 - 18	19- 239	240 or later

Outcome Data Handling

Change from baseline to Week X in outcome endpoints will be calculated as:

- (Outcome Value at Week X) – (Outcome Value at Baseline)

Stratification by Age Group

This study enrolls patients with Netherton Syndrome across a wide range of ages: infants, children, adolescents and adults. Also, for the analysis of the retrospective Part 1 data, a single patient can provide data across several different age groups.

Because Netherton Syndrome may have different manifestations at different ages, selected population characteristics and outcome variables will be analyzed overall and stratified by age group. If not otherwise specified, the planned age groups are the following:

- < 4 years,
- 4 to <6 years,
- 6 to <12,
- 12 to <18,
- 18 years or older

These age groups can be modified prior to the analysis based on the actual distribution of the age in the final enrolled population.

The age at a specific point in time will be calculated based on the age at enrolment by the following formula:

Age at assessment/clinical visit = Age at enrolment – Round ((date of enrolment – date of assessment/clinical visit)/365.25), 1).

All ages will be calculated based on the reported age at enrolment, the year of birth will not be considered for the calculation of ages for the slotting into age groups.

For the analysis of assessments which are retrospectively extracted data of Part 1 and prospectively for the Part 1 + Part 2 patients, the age group will be based on the actual date of the assessment. If patients are observed across different age groups, the patients are included in multiple age groups and the assessments are allocated to the age groups by the calculated age at the date of the assessment.

However, the prospectively collected PROs and ClinROs in Part 2 will be stratified based on the age at enrolment, regardless of whether or not the patient would be falling into the adjacent older age group at a follow-up visit, based on the above formula.

For example, if an 11 years old patient is enrolled in January 2024, the 52 week visit is in January 2025 and the calculated patient age at this point in time is 12 years of age. So, e.g. a flare or other data extracted from the patient charts occurring in January 2025 is counted in the age group 12-<18. However the age group for the analysis of the PROs and ClinROs from the 52 week visits will be based on the age at enrolment, so all PRO and ClinRO assessments of this patient will be counted in the 6 to <12 age group.

For the calculation of summary statistics for the retrospective data other than baseline characteristics and medical history, data will be analyzed starting from the date of the referral to the site until the end of the observational period, i.e. date of death, date last known to be alive or date of enrolment (Part 1 Population), or Week 52 visit (Part1 + Part 2 Population), whatever comes first. Data prior to the date of the referral to the site, if any reported, will be included in the data listings and flagged, but not included in summary statistics.

The calculation of the cut-off dates for the age groups will be based on a calculated date of birth, calculated by the formula:

Calculated date of birth = Enrolment date – 182 days – (round (365.25*age at enrolment), 1).

This formula will be used regardless of whether or not the calculated year of birth is in agreement with the reported year of birth on the eCRF. All analysis will be based on the reported age at enrolment to avoid possible conflicting values between age at enrolment and the reported year of birth, both reported only in full years.

The cut-off date for a specific age group will be calculated as:

Cut-off date = Calculated date of birth + round (365.25* age cut-off)-1.

E.g. the cut-off date between the <4 years and the 4-<6 years age group will be calculated as Calculated date of birth + 4*365.25 – 1 day. This is the last day the patient is counted in the <4 years category and the following day is counted in the 4-<6 year category.

For the calculation of incidence rates in a specific age group the start date of the observational period will be calculated as the lower cut-off date of specific age group + 1 (= first day

counted in this age group) or the date of referral to site, whatever is later. The end date of the observational period is calculated as the upper cut-off date of the specific age group (=last date counted in this age group), date of death, date last known to be alive, or date of enrolment (Part 1 Population), or Week 52 visit (Part1 + Part 2 Population), whatever comes first. If the calculated end date of the observational period is prior to the start date, the patient has no observational period in this age group.

For the overall analysis across all age groups, the start date of the observational period is the date of referral to the site. The end date of the observational period is calculated as date of death, date last known to be alive, or date of enrolment (Part 1 Population), or Week 52 visit (Part1 + Part 2 Population), whatever comes first.

Analysis Populations

Analysis populations will be used for the primary analysis as defined in Section 6.3. However, observations during prior participation in a clinical trial will not be included in the primary analysis. The patients included in the Part1 only and the Part1 + Part 2 Population will analyzed as Overall Population.

Secondary analysis populations are the following and will be used for sensitivity analyses:

- Pure Natural History Population, defined as the primary analysis population excluding the patients who received any off-label use medications or treatment from any expanded access program.
- Pure Natural History Population + Off-Label Patients, defined as the primary analysis population excluding patients who received medications from any expanded access program
- Modified Natural History Population, defined as the primary analysis population including observations from participants during a clinical trial at any time prior to Part 1 or Part 2 participation of the natural history study.

10.1 MAIN ANALYSIS

10.1.1 Protocol Violations and Deviations

Because this is an observational and non-interventional study with no mandatory treatment or assessments, protocol violations are mainly restricted to the violation of the I/E criteria or administrative protocol violations (e.g. providing a signature from a non-authorized staff member). Protocol violations will not be analyzed or summarized as part of the statistical analysis.

10.1.2 Study Population Summary**10.1.2.1 Subject Disposition**

Subjects screened, subjects eligible (based on the I/E criteria), subjects not eligible and the reason subjects were not eligible will be summarized only for the screened population using subject counts. The denominator for calculating the percentages will be the set of screened subjects.

For the Part1 + Part 2 Population, the following measures will be summarized using descriptive statistics:

- Number and percent of patients completing the observational period up to the Week 16 visit
- Number and percent of patients completing the entire observational period up to the Week 52 visit
- Primary reason for not completing the planned observational period.
- Vital status at the end of the study

For subjects enrolled only in Part 1 the vital status at the date of the data abstraction will be summarized using descriptive statistics.

Furthermore, the following measure will be presented as part of the disposition for the Part1 population, the Part1 + Part2 Population, and the Overall Population:

- Time from NS diagnosis until referral to site (years)
- Time from referral to site to enrolment visit or date of death or date patient is last known to be alive, whatever comes first (retrospective observational time in years)
- Patient age at referral to site (analyzed as categorical variable based on the age groups defined above)

10.1.2.2 Socio-Demographic Characteristics

Socio-demographic characteristics will be summarized separately for the Part 1 population, the Part 1 + Part 2 Population and the Overall Population. Socio-demographic characteristics are captured for the point in time at enrolment (or, for deceased patients, at the time of death). The continuous variables of subject age, weight, height, and body mass index (BMI) will be summarized overall and stratified by age group at enrolment as defined above (< 4 years, 4 to <6 years, 6 to <12, 12 to <18, and 18 years or older) using descriptive statistics for continuous variables. Weight will also be summarized for the following categories: ≤60kg, >60 to ≤90kg and >90kg, and BMI will be summarized for the following categories: <25 kg/m², 25 to < 30 kg/m², ≥30 kg/m². The categorical variables of subject sex, gender identity, race, and ethnicity as well as of marital status, educational level, residence at time of diagnosis, relationship of consanguinity, family history of Netherton syndrome (including relationship to the patient) and country of site will be summarized overall and by age group at enrolment using descriptive statistics for each category. Missing categories will be presented if necessary.

10.1.2.3 Baseline Characteristics and Medical History

The baseline characteristics and the medical history will be summarized separately for the Part 1 Population, the Part 1 + Part 2 Population and the Overall Population. The following variables will be summarized:

- Skin type (based on Fitzpatrick scale, categorical data)
- Age at first clinical signs and symptoms as a continuous variable
- Time from first signs and symptoms until the diagnosis of Netherton Syndrome as continuous variable
- Time from diagnosis of NS until date of study enrolment (based on ICF date) in years summarized as a continuous variable and summarized for the following categories: ≤ 1 year, >1 to ≤ 5 years, >5 to ≤ 10 years, >10 yrs.
- Any differential diagnosis prior to Netherton Syndrome diagnosis (Yes/No) and number of differential diagnoses as categorical variables
- Diagnosed condition, based on ICD text (not ICD code) as categorical variable

All other details will be presented in a data listing but not summarized.

The initial diagnosis of Netherton Syndrome will be summarized using descriptive statistics for categorical data as follows:

- Diagnosed condition, based on ICD text
- Physician specialty who made the diagnosis
- Method of diagnosis (select all that apply)
- Clinical Diagnosis Signs and Symptoms (select all that apply)
- Phenotype as categorical variable
- Severity of erythroderma, erythema, scaling, skin thickening, elevated red bumps on the skin, having defined lesions, itch as its worst during diagnosis, pain at its worst during diagnosis (none / mild / moderate / severe / no information in charts)

ICD diagnosis of Netherton Syndrome will also be summarized (Summary of ICD codes with ICD version and ICD text).

Gestational information will be summarized for the patients with available gestational information. For the calculation of percentages, the denominator will be the number of patients with available gestational information. The following measures will be summarized:

- Was colloid membrane present at birth (Yes/No/No information),
- Whether the patient was a preterm birth (Yes/No/No information).
- Gestational age at birth
- Birth weight

- Birth length
- Ability to breastfeed (Yes/No/No information)
- Neonatal allergy to cow's milk (Yes/No/No information)
- Failure to thrive (Yes/No/No information)
- Time from first onset of signs and symptoms until diagnosis of failure to thrive (calculated as date failure to thrive was observed or diagnosed – date of onset of first signs and symptoms)/30.4.
- Complications during delivery or at birth (Yes/No/No information)
- Type of complication (select all that apply, denominator for the calculation of percentages is the number of patients with gestational information).

Lifestyle habits will be summarized as follows stratified by the age groups <18 years versus ≥18 years of age:

- Any substance use documented in the records (if 'No' input the missing values for the use of the individual substances by 'Never')
- Use of tobacco (Never/current/former/no information available, and duration of use in years)
- Use of nicotine (Never/current/former/no information available, and duration of use in years)
- Use of caffeine (Never/current/former/no information available, and duration of use in years)
- Use of cannabis (Never/current/former/no information available, and duration of use in years)

10.1.3 Primary Outcome Analysis

Primary end point is the clinical assessment of severity of Netherton Syndrome using the IASI score. The assessment will be conducted in the clinic for the patients participating in Part 1 + Part 2 at enrolment, 2 weeks, 16 weeks, and 52 weeks after enrolment. The total score (range 0-48) and the sub-scores of erythema and scaling (range 0-24) will be summarized using summary statistics for continuous variables for each visit and for the changes from enrolment. Higher scores indicate worse clinical severity, so negative changes indicate improvements, and positive changes indicate worsening. The analysis will be purely descriptive, and no statistical hypothesis will be tested. The analysis will be performed overall and stratified by age group (based on the age at enrolment). In addition, the number and percentages of patients who have a decrease in the IASI score of 50% or more, based on the assessment at baseline, will be reported including 95% CIs.

Values prior to enrolment will be included in the data listing for all participants and summarized separately from the Part 2 data, stratified by age group. All assessments of a

patient will be included in this analysis, even if there are multiple assessments from a single patient in one age group.

10.1.4 Secondary outcome analysis

Secondary end point is the clinical assessment of severity of Netherton Syndrome as assessed by the IGA. IGA is a ClinRO assessing the global severity of erythema and scaling in Netherton Syndrome patients using a 5-point Likert scale ranging from 0 (=clear) to 4 (=severe). The IGA score will be summarized for each visit (enrolment, week 2, week 16, and week 52) using frequency tables. The changes from enrolment will also be summarized using frequency tables where positive changes will indicate a worsening in severity and negative changes indicate improvement. The analysis of the IGA will be purely descriptive and no hypothesis will be tested. The analysis will be performed overall and stratified by age group at enrolment. Values prior to enrolment will be included in the data listing for all participants but not summarized.

To analyse the consistency between the IGA and the IASI score, the IASI score will be summarized for each category of the IGA using descriptive statistics for continuous variables. Furthermore, the consistency between the IGA and the IASI will be graphically presented by scatter plots of the IASI score in each IGA category. These analyses will be performed for the enrolment, week 16, and the week 52 visit.

Consistency of the changes from baseline to week 16 and week 52, changes in the IASI score will be summarized for each category of changes in IGA and also presented graphically by scatter plots.

10.1.5 Further Outcome Analysis

10.1.5.1 Phenotype

The phenotype will be extracted from the patient charts starting from the initial diagnosis of NS up to the study end date (defined as enrolment for Part 1 participants and the week 52 visit for Part 1 + Part 2 participants), lost to follow-up, or death, whatever comes first. For the retrospective data, i.e. assessments prior to the enrolment date, the phenotype will be summarized stratified by age group. If a patient has multiple assessments within an age group, the first assessment is used in each age group and compared to the last assessment in the same age group. For the patients who are observed across different age groups, the phenotype in the actual age group will be compared with the phenotype in the previous age group using cross tabulations. For the youngest age group, first and last phenotype will be compared within this age group instead.

For the Part 2 participants, the phenotype will be summarized stratified by age group and overall at enrolment, the Week 2, Week 16, and Week 52 assessment. Changes over time will be summarized using cross tabulations of the enrolment visit with the Week 2, the Week 16, and the Week 52 visit.

10.1.5.2 Netherton Syndrome Complications and Co-Morbidities

Netherton syndrome complications and co-morbidities will be derived from the Co-Morbidities / Netherton Syndrome complication page. Netherton Syndrome complications and co-morbidities will be combined for the analysis. NS-complications and co-morbidities are captured between the initial diagnosis of NS up to the study end date (defined as enrolment for Part 1 participants and the week 52 visit for Part 1 + Part 2 participants), lost to follow-up, or death, whatever comes first.

Aside of the pre-specified NS complications and co-morbidities in the eCRF, the following conditions are of special interest:

- Acne
- MI/Heart attack
- Stroke
- QT prolongation
- Peripheral neuropathy
- Hepatic failure/ hepatic issues
- Renal failure
- All infections
 - Mucocutaneous
 - Categorization of pathogens (if data exists)
- All malignancies
 - Skin malignancies

For the retrospective Part 1 data, the number and percentages of affected patients, including 95% CIs, will be summarized for each condition/diagnosis stratified by age group and overall using frequency statistics. The condition will be counted in a specific age group if the date of diagnosis is prior to or at the last date the patient is in this age group and the condition is either ongoing or the end date of the condition is after the first date the patient is in this age group. Ongoing conditions will be counted in all age groups from the start date of the condition up to the age group the patient is at the end of the study. If at least the year of the diagnosis of the complication is known, the complication is counted in the appropriate age group. If date of diagnosis is completely unknown, it is assumed that the complication is diagnosed at the date of the referral to the site.

For the Part 1+Part2 participants, the frequency of each condition will also be reported for the enrolment, the 16-week and the 52-week visit. This analysis will be performed stratified by age at enrolment and overall.

Two different types of incidence rates will be calculated for each condition: Incidence rate based on time to first event and recurrent event rate. For the calculation of the incidence rate based on time to first event (for patients who had an event) the observational period is the time from enrolment up to the date of the first event. For patients without event, the observational period is the time from enrolment up to the study end date. The incidence rate is calculated as the number of patients with at least 1 event divided by the total person-time as defined above.

The recurrent event rate will be calculated as number of events divided by the total person-time across all patients. A subsequent event will be counted as re-current event if the previous event is not ongoing and the start date of the subsequent is after the end date of the previous event.

Percentages of affected patients, incidence rate based on first event and recurrent event rate will also be calculated in the primary population (i.e. meeting the IC/EC) and sensitivity analyses with the Pure natural History Population, the Pure Natural History Population + Off Label Patients, and the Modified Natural History Population.

Percentages of each of the above conditions being treated and percentages of the condition as ongoing or resolved will be calculated for the conditions reported in Part 2. Denominator is the number of each reported conditions (not number of affected patients). , All other details will only be presented in a data listing. Depending on the available data, further explorative analyses can be performed as deemed meaningful.

Allergies and intolerances reported for the Part 1 and the Part 1 + Part 2 patients will further be analyzed by type of allergy (allergen) using frequency tables. Number and percentages of patients affected each allergen will be calculated Also the number of allergens per patient will be analyzed as a continuous variable and for the following categories: No allergy, 1, 2, 3, and >3 allergens.

Also type of infection (bacterial, fungal, viral, other) and whether the infection is a mucocutaneous infection will be analyzed using frequency tables. Denominator is the number of reported infections. Additionally, the number of infections during the prospective observational period (enrolment to Week 52) will be analyzed as a continuous variable for the Part1+Part 2 participants.

10.1.5.3 Treatment patterns

Treatment patterns (medical treatments, procedures, and non-drug treatments) will be analyzed for the treatments of NS. Treatments for reasons other than NS will be listed but not summarized. Treatment pattern will be analyzed for the patients in Part 1, Part 1 + Part 2, and overall.

Medical treatments will be coded using WHODrug Global B3 September 1, 2023 or a later version.. Frequency statistics will be calculated on chemical/therapeutic/pharmacological subgroup (ATC level 4) by age groups and overall. A medication will be counted in a specific age group if the drug is taken at any time during the age of the age group, regardless of the start or end date of the drug. Specifically, the number and percentage of patients who are treated with retinoids, systemic steroids, immunoglobulins, biologics or any other immunosuppressant will be reported in a separate table stratified by age group and route of administration and overall. Medications will also be reported by route of administration using a frequency table. Also, the number and percentages of patents who initiated these medications from enrolment up to Week 52 will be reported. Medical treatment will also be

summarized by type of medication (prescription drug, over-the-counter drug, investigational drug).

Duration of medical treatment will be calculated on therapeutic/pharmacological subgroup (ATC level 3) to avoid small sample sizes. Duration will be calculated by age group and overall. For the calculation of the duration in a specific age group, the start date will be calculated as the maximum of the start date of the medication and the first date the patient is in this age group. The end date of the medication is the minimum of the end date of the medication and the last day the patient is in this age group. Duration of treatment will also be presented for the above mentioned medications.

The reason for treatment discontinuation will be summarized on therapeutic/pharmacological subgroup (ATC level 3) by age group and overall. For the analysis on age group, the medication is counted in the age group the medication is discontinued (e.g. a medication is started at the age of 3 and discontinued at the age of 5 years, so the reason for discontinuation is counted in the age group 4 to <6 years. The reason for treatment discontinuation will also be reported for the above mentioned medications.

All medical treatments reported on the Medical Therapy page will also be presented in a data listing.

The type of the procedures and non-drug treatments for Netherton syndrome will be summarized by age group and overall. Type of treatment will also be summarized stratified by reason for the procedure (Recurring routine clinical management, One-time treatment, Urgent care for flare-up). Reason for discontinuation of non-drug treatments will be summarized stratified by type of treatment, and age group, as described for the medical treatments. Depending on the available data, further explorative analysis will be performed as deemed appropriate.

10.1.5.4 Dietary History

Dietary history will be summarized similarly as the treatment patterns. Method of assistive feeding will be summarized by age group and overall. Duration of assistive feeding will be calculated by method and overall. Overlapping periods of assistive feeding methods across different methods will be included only once in the overall analysis. All other details will be presented in a data listing but not summarized.

10.1.5.5 Healthcare Resource Utilizations

Healthcare resource utilizations (HCRU) will be summarized only for the prospectively recorded data of the Part1 + Part 2 participants. HCRUs prior to enrolment (Part 1 and Part 1 + Part 2 participants) will be listed but not summarized.

The frequency and incidence rate of outpatient visits, calculated as number of outpatient visits per year will be summarized by age group and overall using descriptive statistics for continuous variables. Incidence rate will be calculated as the number of outpatient visits divided by the Follow-up period i.e. the period from enrolment up to the 52 week visit (or date of study discontinuation, whatever comes first). The type of specialist will be summarized by age group and overall using frequency tables.

The frequency and incidence rate of emergency department visits, calculated as number of emergency department visits per year will be calculated and summarized by age group and

overall. The frequency and incidence rate of telehealth visits and phone consultations will be calculated in a similar way.

The frequency and incidence rate of hospital admissions and admissions to the ICU will be reported by age group and overall. Prospectively versus retrospectively reported data will be stratified based on the admission date, i.e. the prospectively recorded hospital admissions are all hospital admissions with an admission date on or after the enrolment date. Summary statistics for the duration of a single hospital and ICU admission and for the number of days in hospital or ICU per year will be summarized by age group and overall. The duration of a single hospital admission will be calculated as date of discharge – date of admission + 1 day, regardless of whether or not there is an overlapping period of an ICU admission. The number of days per year in hospital will be calculated as numbers of days in hospital in the analysis period (multiple hospital admissions will be summed) divided by the number of days of the prospective observational period * 365.25 days.

10.1.5.6 Flare and Flare Characteristics

Flares and flare characteristics will be analysed from the reported flare characteristics data in the eCRF. All analyses of flares and the flare characteristics will be performed separately for the retrospective data from the Part 1 and Part1 + Part 2 patients and for the prospectively reported data from the Part 1 + Part 2 patients. The frequency and incidence rate of flares will be summarized in the same way as the incidence rate of hospitalizations as numbers of flares per year. The observational period for Part 1 is the time frame from the referral to the site up to the date of enrolment. The observational time for Part2 is the time span from enrolment up to the Week 52 visit (or date of study discontinuation, whatever comes first). The incidence rate of flares will be analysed for 3 different periods: 1) from enrolment up to week 16, from Week 16 up to Week 52, and from enrolment up to Week 52. Flares will be stratified as prospectively versus retrospectively reported flares based on the onset date of the flare. The incidence of flares will be summarized by age group and overall.

Outcome of the flares (resolved, resolved with sequelae, severity decreased) will be summarized stratified by age group and overall using frequency tables. The median duration of flares will be analyzed using a Kaplan-Meier approach where flares which are not classified as resolved or resolved with sequelae will be counted as censored observations at the end of study participation date (as documented on the study end page). Multiple flares in a single patient will be included and analysed independently (analysis per flare). Depending on the percentages of unresolved flares, summary statistics for the duration of the resolved flares will be provided.

Flare characteristics (type and severity of symptoms, potential cause, and management of flairs) will be summarized stratified by age group and overall using frequency tables.

All flares and flare characteristics will also be presented in a data listing.

10.1.5.7 Analysis of the Additional Clinical Outcome Assessments

Additional clinical outcome assessments will be performed in the Part1 + Part 2 population at enrolment, and 16weeks and 52 weeks thereafter. These instruments are not expected to have been used in routine clinical care and will not be analyzed in the Part1 population or the Part1 + 2 Population prior to enrolment.

10.1.5.7.1 Netherton Area Severity Assessment (NASA)

The NASA score is ages and will be analysed stratified by age group and overall in the same way as the IASI score as a continuous variable.

10.1.5.7.2 Face, Legs, Activity, Cry, Consolability Scale (FLACC)

The FLACC is assessed in infants up to 2 years of age. The FLACC will be analysed only overall in the same way as the IASI score as a continuous variable.

10.1.5.7.3 Scalp Hair Assessment

The scalp hair assessment score is assessed in patents 12 years or older. The Scalp hair assessment score will be analysed only overall in the same way as the IASI score as a continuous variable.

10.1.5.7.4 5-D itch scale

The 5-D itch scale is a multidimensional questionnaire designed to assess itching. The five domains of the questionnaire include: degree, duration, direction, disability, and distribution. The duration, degree and direction domains include one item each, and the disability domain had four items. All items of the first four domains were measured on a five-point Likert scale. The distribution domain includes 16 potential locations of itch, including 15 body part items and one point of contact with clothing or bandages. For the distribution domain, the number of affected body parts is tallied (potential sum 0–16) and the sum is sorted into five scoring bins: sum of 0–2 = score of 1, sum of 3–5 = score of 2, sum of 6–10 = score of 3, sum of 11–13 = score of 4, and sum of 14–16 = score of 5. The 1 item domain of degree, duration and direction, the 4 items of the disability domain and the tailed score of distribution will be analysed in the same way as the IGA Score as categorical variables. The change from enrolment visit will not be analysed for the dimension of direction.

10.1.5.7.5 Itch NRS & PROMIS PIQ-C

Itch NRS and PROMIS PIQ-C will be used for different age groups. The Itch NRS measurement will be used in patients who are at least 12 years of age. Parent-report/proxy versions of PROMIS PIQ-C (Short Form 6a) will be used to assess severity of itch in patients aged 1–7 years. Paediatric self-report version of PIQ-C will be used in patients aged 8–11. Therefore, the analysis of the Itch NRS & PROMIS PIQ-C will be performed for the following groups:

- Patients assessed by the PROMIS PIQ-C (short form 6a), representing patients 1-7 years of age
- Patients assessed by the paediatric self-reported version of PROMIS PIQ-C, representing patients 8-11 years of age
- Patients assessed by the Itch NRS, stratified by the following age groups:
 - <18 years of age

- Older than or equal to 18 years of age

The scores will be analysed in the same way as the IASI score as continuous variables in the above age groups and overall.

10.1.5.7.6 Pain NRS & FPS-R

The pain NRS is a one-item 11 point rating scale to assess the worst pain experienced in the last 24 hours and is used in patients 12 years or older. The Pain NRS will be summarized by age group and overall in the same way as the IASI score as a continuous variable. All patients with a calculated age of younger than 12 years of age will also be included in the 12-<18 year category.

The Face Pain Scale-Revised (FPS-R) will be used for infants from 3 to 11 years of age and will be analysed by age group and overall in the same way as the IGA score as categorical variables. All patients with a calculated age of 12 years and older will also be included in the 7 - < 12 year category.

10.1.5.7.7 DLQI/CDLQI

The DLQI is a patient-reported assessment tool to evaluate the impact of dermatologic condition on patient's quality of life. The scale contains 10 questions and its total score ranges 0–30. Higher scores indicate worse outcome, and the score can be interpreted with established cut-off categories: 0 (score of 0–1), no effect; 1 (score of 2–5), small effect; 2 (score of 6–10), moderate effect; 3 (score 11–20), very large effect; 4 (score 2–30), extremely large effect. DLQI will be used in patients who are at least 16 years of age.

A children's version of DLQI is available to patients aged 4–15 years old (CDLQI), including a cartoon version for young children.

For the DLQI, frequency tables for the established cut-off categories will be presented for the enrolment, week 2, week 16, and the week 52 visit overall and stratified by the following age groups:

- Children's version aged 4-<7 years
- Children's version 7 years or older (representing children from 7 to 15 years of age)
- Adult version (representing patients 16 years or older)

The score of the DLQI/CDLQI will also be analysed as a continuous variable as described for the IASI score above.

10.1.5.7.8 PGI-S for erythema and PGI-S for scaling

PGI-S for erythema and PGI-S for scaling are single items that assess the severity of erythema and scaling on an ordinal scale: "None", "Mild", "Moderate", "Severe" and "Very Severe".

The PGI-S erythema and the PGI-S scaling will be used in patients 12 years of age and older. The PGI-S erythema and the PGI-S scaling will be analysed by following age group and overall in the same way as the IGA score.

- <18 years of age
- 18 years or older

10.1.5.7.9 Hospital Anxiety and Depression Scale (HADS)

HADS is a validated scale for assessing anxiety and depression in general hospital setting. It has 14 items in total (each scoring from 0 to 3), which constitute the overall distress scale (HADS-S). The highest possible score for HADS-S is 42, and a score over 9 is considered as distress.

HADS can be scored based on 7 items on anxiety to form the anxiety subscale (HADS-A) and 7 items for the depression subscale (HADS-D). The categorisation of severity for both HADS-A and HADS-D subscales are mild (scores 8–11), moderate (scores 12–15), severe (scores 16–21); 21 is the highest score for each subscale. The HADS scale will be used in patients who are at least 12 years of age.

The overall distress score will be analysed by age group and overall in the same way as the IASI score as a continuous variable. Additionally, the number and percentages of patients who suffer from distress (total score of 9 or above) will be presented for each visit.

The subscales HAS-A and HAD-D will be analysed based on its categorization of severity by age groups <18 years of age and 18 years or older and overall in the same way as the IGA score as categorical variables. Both subscales will also be analysed as a continuous variable as described for the IASI score above.

10.1.5.7.10 Medical Outcome Study Sleep Scale (MOS) and PROMIS Sleep Disturbance

MOS sleep scale is a 12-item patient-reported scale to evaluate sleep disturbance in a 4-week timeframe. Using the MOS sleep scale, patient subjectively evaluates experiences in six different domains of sleep impairment: disturbance, snoring, short of breath or headache, adequacy, somnolence and quantity. The subscales and the global index are calibrated on a 0 to 100 scale. A lower MOS scores corresponds to a higher level of sleep impairment. The MOS sleep scale will be used in patients who are at least 18 years of age.

The subscales and the global index will be analysed in the same way as the IASI score as continuous variables.

The PROMIS Sleep Disturbance short form 4a:

- Paediatrics self-report version will be used in patients 8–17 years old.
- Parent-report/proxy version will be used in patients of 1–7 years old.

The PROMIS Sleep Disturbance Short Form consists of 4 questions, rated from 5 (Never) to 5 (Always). The PROMIS Sleep Disturbance Short form will be analysed stratified by version (self-reported or parent proxy) in the same way as the IGA score as categorical variables.

10.1.5.8 Work Productivity and Activity Impairment Questionnaire – Specific Health Problem (WPAI SHP) for Patients and Adult Caregivers

Adult patients (aged 16 and above) and adult family members who are the primary carer of a paediatric patient will be asked to complete the 6-item WPAI-SHP to assess the hours missed from work due to a health condition in the past seven days and the degree of decreased

productivity and performance of daily activities are measured on a horizontal scale of 0 (had no effect) to 10 (completely prevented me from working or doing daily activities).

The WPAI-SHP yields four types of summary scores: Absenteeism (total hours of work missed), Presenteeism (total hours impairment at work or with reduced productivity), Overall work productivity loss, and Activity impairment.

The WPAI will be analysed separately for the adult patients and the primary caregivers of paediatric patients. The caregiver WPAI will be analysed stratified by patient age and overall. The WPAI for adult patients will be analysed overall.

The 4 scores of absenteeism, presenteeism, overall productivity loss, and activity impairment will be analysed in the same way as the IASI score as continuous variables.

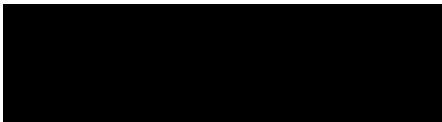
10.1.5.9 Family Dermatology Life Quality Index (FDLQI)

The FDLQI is a 10-item questionnaire designed to measure the burden on adult family members (at least 16 years of age) of patients with a skin condition. Each question is scored on 0 to 3; the total score is calculated by summing the score of each question (i.e., maximum = 30 and a minimum = 0). The total score will be expressed as a percentage of the maximum possible score of 30 (standardized score = raw score/30 * 100). A higher total score denotes a worse impairment in quality of life for the family member due to the patient's disease condition.

The standardized FDLQI score will be analysed stratified by the age group of the patient in the same way as the IASI score as a continuous variable.

10.1.5.10 Vital signs

Vital signs will be summarized for the enrolment, Week 16, and the Week 52 visit. Changes from the enrolment to the Week 16 and the Week 52 week will also be summarized using descriptive statistics.



10.3 SAFETY ANALYSIS

N/A

11. QUALITY CONTROL

According to the [REDACTED] SOPs, all analysis datasets, tables and listings will be double programmed and reviewed by the trial statistician.

12. REFERENCES

12.1 PUBLISHED REFERENCES

12.2 UNPUBLISHED REFERENCES

