Statistical Analysis Plan

KCC-DN-001, Clinical Investigational Plan Version 1.0, dated 11 September 2019

Effect of use of DryNites® absorbent pants on the rate of spontaneous resolution of paediatric nocturnal enuresis (NE)

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0, 03Feb2020 for Clinical Investigation Plan KCC-DN-001.

The statistical analysis plan (SAP) signature page applies to both SAP text and SAP Templates (outputs shells or Tables/Listings/Figures (TLFs) shells). Templates must be sent to the customer with the first draft SAP text.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorised Version
0.1	20Dec2019	Sara Colli	Not Applicable – First draft
1.0	24Jan2020	Sara Colli	Extrinsic and Intrinsic Paediatric Incontinence Questionnaire (PinQ) items completed. Removed signature for Aarhus University Hospital, only Kimberly-Clark will sign the document.
1.0	03Feb2020	Sara Colli	Formal updates post QC and senior review. Safety set definition updated to include also subjects screened as exposed to DryNites®. Treatment emergent adverse events definition updated to include all events occurred or worsened on or after first use of DryNites®.

			Safety set and treatment emergent adverse event definitions were noted in the change from protocol section as different from protocol.

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1. ABBREVIATIONS

AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CI	Confidence interval
CIS	Checklist Individual Strength
CRF	Case report form
CRO	Contract research organisation
EAS	Extension analysis set
eCRF	Electronic case report form
EDC	Electronic data capture
ICF	Informed consent form
LSMean	Least squares means
MAR	Missing at random
MDI	Medical device incident
MedDRA	Medical Dictionary for Regulatory Activities
NE	Nocturnal enuresis
PAS	Primary analysis set
PDSS	Paediatric Daytime Sleepiness Scale
PinQ	Paediatric Incontinence Questionnaire
PRO	Patient-reported outcome

PT	Preferred term
QoL	Quality of life
RND	Randomised set
RWES	Real-World Evidence Solutions
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis system
SCR	Subject screened set
SD	Standard deviation
SOC	System organ class
TEAE	Treatment emergent adverse event
TLF	Tables/Listings/Figures
WHOQoL-BREF	World Health Organization Quality of Life BREF

2. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of equivalence in spontaneous resolution of nocturnal enuresis (NE) in children, between discontinuation of nocturnal use of absorbent pants, compared with continued use of absorbent pants, over a period of 4 weeks. It describes the data to be summarised and analysed, including specifics of the statistical analyses to be performed.

This SAP is based on clinical investigation plan version 1.0, dated 11 February 2019 and case report forms (CRFs) version 1.0, dated 29 October 2019

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to determine if discontinuing the use of DryNites® absorbent pants over a period of 4 weeks has any impact on the rate of spontaneous resolution of NE compared with continuing use of DryNites® absorbent pants.

3.2 Secondary Objectives

The secondary objectives are:

- to determine if using DryNites® absorbent pants improves the child's Quality of Life (QoL) assessed by the Paediatric Incontinence Questionnaire (PinQ) compared with not using absorbent pants;
- to determine if using DryNites® absorbent pants improves the parent/carer's QoL assessed by the World Health Organization Quality of Life BREF (WHOQoL-BREF) compared with not using absorbent pants;

- to determine if using DryNites® absorbent pants improves the child's sleep assessed by the Paediatric Daytime Sleepiness Scale (PDSS) compared with not using absorbent pants;
- to determine if using DryNites® absorbent pants improves the parent/carer's sleep assessed by the Checklist Individual Strength questionnaire (CIS) compared with not using absorbent pants;
- to determine if DryNites® absorbent pants offer different benefits or limitations to previously used absorbent pants/nappies.

3.3 Exploratory Objective

The exploratory objective is to describe data collected over the extension period.

3.4 Safety Objectives

The safety objectives are:

- to describe all Adverse Events (AE) reported since informed consent form (ICF) signature, throughout the patients' discontinuation of the study;
- to describe Treatment Emergent Adverse Events (TEAE);
- to describe Serious Adverse Events (SAE);
- to describe Medical Device Incidents (MDI).

4. STUDY DESIGN

4.1 General Description

This is an 8-week randomised, open-label, 2-arm, parallel-group Phase IV trial with a 2:1 allocation ratio for discontinuation of continuation of use of DryNites® absorbent pants in children with NE, with an optional 4-week extension period.

Eligible patients will be children with monosymptomatic NE, not previously treated for NE, and managed with absorbent pants/nappies (any brand) for a minimum of 6 months. Participants must be dry at day for at least 6 months. Participants will be divided in 2 age groups of similar size. The younger age group will be comprised of participants aged 4–<6 years old and the older age group will be comprised of participants aged ≥6–8 years old.

One hundred and twenty participants should be recruited, balanced between the 2 age groups. The equivalence margin is set to 2/7 wet nights with an expected proportion of 0.95 and 0.80 wet nights, respectively for continuing and discontinuing use of absorbent pants group. The power is set to 99%.

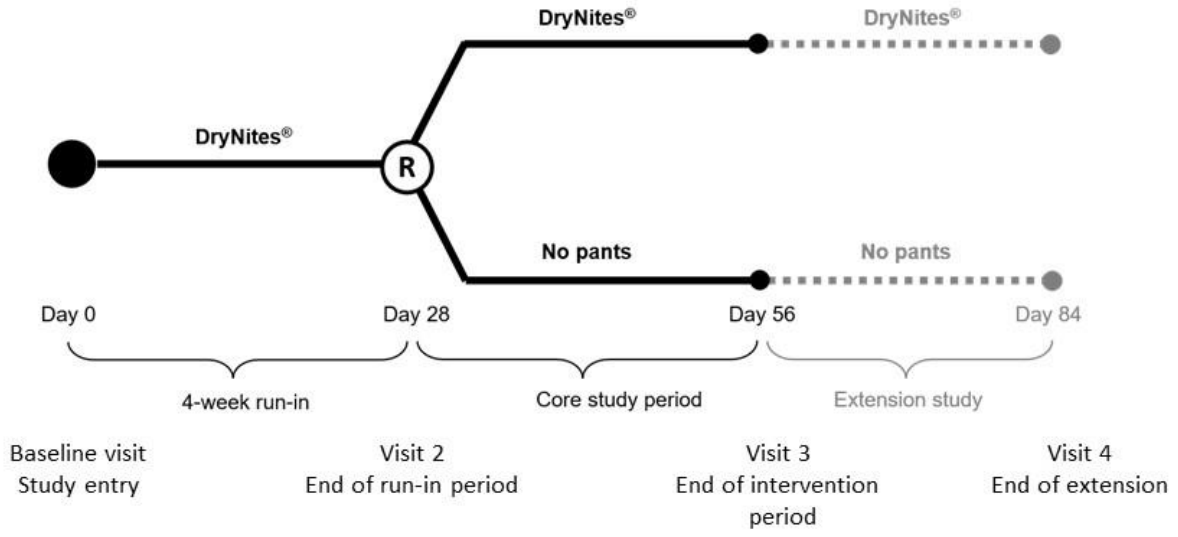
The study consists of 3 consecutive periods of 4 weeks each, including the run-in, the intervention (core trial) period, and the extension period.

Participant meeting the eligibility criteria will enter 4-week run-in period, when all participants will be assigned to using DryNites® every night.

Participant meets the inclusion criterion of NE 7 nights per week during the last week of the run-in period will be randomised to participate in 4-week intervention (core trial) period. Participants will be assigned to either stopping the use of absorbent pants or continuing DryNites® in a 2:1 ratio.

Following completion of the 4-week intervention period, participants will be invited to participate in the optional 4-week extension when participants will remain on their randomly assigned treatment for an additional 4 weeks.

Figure 1



4.2 Schedule of Events

The schedule of events can be found in Section 4.7 of the protocol.

4.3 Changes to Analysis from Protocol

Concomitant medications will be collected in relation to adverse events and medical device incidents only. For this reason, the summary of concomitant medication will be provided on randomised analysis set only as no data will be collected for patients screened and not randomised.

Safety set definition will be modified to include all patients exposed to DryNites for at least 1 night after signature of informed consent.

Treatment emergent adverse events will be defined as all events occurred or worsened in severity after the start of the screening period.

5. PLANNED ANALYSES

5.1 Interim Analysis

Not applicable

5.2 Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Real-World Evidence Solutions (RWES) Biostatistics following Sponsor Authorisation of this Statistical Analysis Plan.

The analysis on primary and secondary endpoints will be performed once the last randomised patients will complete the intervention period. At the time of this analysis the database will not be locked if at least one participant is still ongoing on extension study period.

The full set of analyses will be updated, when applicable, after the official database lock, occurring after the completion of the Visit 4 by the last patient accepting to participate to the extension period.

6. ANALYSIS SETS

6.1 All Patients Screened Set

The all screened (SCR) set will contain all patients who provide informed consent for this study.

6.2 Randomised Set

The randomised set (RND) will contain patients in the Screened Set who are assigned to a randomisation group.

6.3 Safety Analysis Set

The safety analysis set (SAF) will contain all patients exposed to DryNites® for at least 1 night after signature of informed consent.

6.4 Primary Analysis Set

The primary analysis set (PAS) will contain all patients in the Randomised Set excluding participants with major violations of the clinical investigation plan.

The following violation will be considered as major:

- Absorbent pants/nappies (of any brand) used nocturnally in the 'no pants' group (≥3 nights showing violation of the clinical investigational plan over the 4-week trial period will merit exclusion; these will be documented in the diary)
- No pants, or absorbent pants of a different brand, used nocturnally in the DryNites® group (≥3 night showing violation of the clinical investigation plan over the 4-week trial period will merit exclusion; these will be documented in the diary)
- Bed mat not used (≥3 nights showing violation of the clinical investigation plan over the 4-week trial period will merit exclusion; these will be documented in the diary)
- Initiation of a prescribed therapy for NE (pharmacologic or bed alarm).

6.5 Extension Analysis Set

The extension analysis set (EAS) will contain all patients in the Randomised Set who participate in the extension period.

7. GENERAL CONSIDERATIONS

Continuous variables will be reported as mean (and standard deviation [SD]) along with median and range where appropriate.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to 1 decimal place while the SD will be reported to 2 decimal places.

Categorical variables will be summarised as number and proportion of the total study population, and by age subgroups (4–<6 years and ≥6–8 years) where appropriate.

In general, descriptive statistics of quantitative parameters (result and change from baseline) by scheduled visits will be provided on observed cases, that is, patients having non-missing assessments at a specific visit. Percentages will then not include the missing category, but the count of missing observations will be provided. Percentages will be presented to 1 decimal place except percentages equal to 100 that will be presented as 100% and zero frequencies that will be presented as 0%.

Confidence intervals (CI) and statistical tests will be 2-sided unless otherwise specified. P-values, which are greater than or equal to 0.0001, and less than or equal to 0.9999, will be presented to 4 decimal places. All other p-values, which are less than 0.0001, will be presented as <0.0001.

Individual patient data will be presented in listings considering the Screened Set.

Descriptive analyses will be performed on the SCR Set and the RND Set to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. If more than 15% of randomised participants will be excluded from the PAS, the baseline descriptive analysis will be repeated on the primary endpoint analysis population.

7.1 Reference Start Date

Reference start date is defined as the day of the randomisation and will appear in every listing where an assessment date or event date appears.

7.2 Baseline

Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, but AEs and medications commencing on the reference start date will be considered post-baseline.

7.3 Windowing Conventions

The following table describes assignment of visit windows to the following data for purposes of analysis:

Table A: Windowing

Assigned Study Day (Inclusive)		**Visit Assigned**
From	**To**	
-35	0	Visit 1
1	1	Visit 2
2	42	Visit 3

43	63	Visit 4

To define cut on visits to the patient's diary, visit date will be used as reference along with windowing conventions.

7.4 Common Calculations

For quantitative measurements, change from baseline will be calculated as:
(Test Value at Visit X – Baseline Value).

The effect size will be calculated as:
[(Test Value at Visit X – Baseline Value)/ Baseline SD].

7.5 Software Version

All analyses will be conducted using Statistical Analysis System (SAS) version 9.4 or higher.

8. STATISTICAL CONSIDERATIONS

8.1 Statistical Tests and Confidence Intervals

Unless otherwise specified in the description of the analyses, a two-sided 95% CI will be considered as a default (alpha= 5%). The equivalence margin is set to 2/7 wet nights with an expected proportion of 0.95 and 0.80 wet nights, respectively for continuing and discontinuing use of absorbent pants group.
No confirmatory testing is planned, p-values are provided as descriptive representations of the data.

8.2 Adjustments for Covariates and Factors to be Included in Analyses

The baseline of any applicable Patient Reported Outcomes (PRO) will be used as covariate in the analysis of covariance (ANCOVA) planned on secondary endpoints analysis.

8.3 Missing Data

Should missing data occur, the data will be analysed as recorded in the electronic CRF (eCRF), that is, analyses will be performed on patients with non-missing values. However, the amount of missing values for data elements will be reported, and the likely impact of missing data on the analysis and the pattern of the missing information will be assessed.

Depending upon the amount of missing data, and whether there is evidence of bias in the missing data (e.g., differences between patients with and without missing data), multiple imputation (detailed in Section 15.1.2), may be performed and a sensitivity analysis will be carried out comparing the results from the complete case analysis (where records with missing data will be dropped) and the full set analysis including the imputed data.

Missing safety data will not be imputed. Partial date handling is described in Appendix 2.

8.4 Examination of Subgroups

Subgroup analyses will be conducted considering the age group stratification factor at randomisation.

9. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary TLFs to be provided by IQVIA RWES Biostatistics.

10. DISPOSITION AND WITHDRAWALS

The total number of patients included in each analysis set described in Section 6 along with the number of patients for each of following categories will be provided as disposition analysis:

- Patients consented, overall and by age group (4–<6 years and ≥6–8 years)
- Patients randomised, overall and by age group (4–<6 years and ≥6–8 years)
- Patients who completed the 4-week intervention period, overall and by age group (4–<6 years and ≥6–8 years)
- Patients who entered the extension period, overall and by age group (4–<6 years and ≥6–8 years)
- Patients who completed the extension period, overall and by age group (4–<6 years and ≥6–8 years)
- Time and reasons for discontinuation of the study, overall and by age group (4–<6 years and ≥6–8 years).

For all categories except the Screened Set, the percentages will be calculated using the number of randomised patients as the denominator for each treatment group.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics, including characteristics of NE (as collected on eCRF), will be presented for the SCR and RND set.

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of consent
- Sex

- Race
- Ethnicity
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2)
- BMI as category

11.1 Derivations

- Age (years) will be derived in using Month and Year of Birth, and calculated relative to ICF signature, as follows:
  - Age (years) = (ICF Signature year - Birth year) if ICF Month ≥ Birth Month,
  - Age (years) = (ICF Signature year - Birth year - 1) if ICF Month < Birth Month.
- Calculated age will be classified as per randomisation stratum as:
  - 4–<6 years;
  - ≥6–8 years;

  Edit checks were included in the EDC to avoid wrong stratum selection but in case of difference between the calculated stratum and the one used at randomisation, the violation might be considered as reason for exclusion from the PAS.
- Time to discontinuation in weeks = (End of study date – ICF date +1)/30.5;
- Weight (kg) = weight (pounds)*0.453592;
- Height (cm) = height (inches)*2.54;
- BMI (kg/ m^2) = weight (kg)/ height (m)^2;

- Calculated BMI will be classified as follows based on comparison with country specific reference data:
  - Underweight (<5th percentile for sex and age),
  - Normal (from 5th to less than 85th percentile for sex and age),
  - Overweight (from 85th to less than the 95th percentile for sex and age),
  - Obese (≥ 95th percentile for sex and age).

12. MEDICAL HISTORY

Medical History information will be summarised for the SCR and RND set, including both prior and concomitant events collected at Visit 1.

Medical History will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) available at the time of the analysis and will be presented by SOC (System Organ Class) and PT (Preferred Term).

13. MEDICATIONS

Only medications administered to treat an AE or MDI will be collected and will be considered all concomitants.

Therapies will be presented for the SAF set and coded using Anatomical Therapeutic Chemical (ATC) Classification System.

14. STUDY MEDICATION EXPOSURE

Not applicable.

15. Primary Outcome

Direct- to-patient data will be analysed descriptively at each assessment along with applicable change from baseline on the RND and PAS.

15.1 Primary Analysis

The primary analysis will be performed separately for age groups for the PAS comparing the 95% CI for the difference between the means of average wet nights at the end of intervention period for the 2 groups with the predefined margin. Being the primary analysis focused on last week of the intervention period (lasting from randomisation to Visit 3) and the equivalence margin reported as 2/7 (two nights over a week), the average number of wet nights was chosen as reliable outcome on primary endpoint.

15.1.1 Primary Analysis Variable & Derivation

The primary analysis variable will be the difference between the 2 groups on the average number of wet nights in Week 4 of the intervention study period and will be derived using the item "Did the child have an NE (nocturnal enuresis) event?" collected on daily diary. The number of "Yes" for each patient will be counted over the last 7 days of the intervention period (from randomisation till the Visit 3 day).

15.1.2 Missing Data Methods for Primary Analysis Variable

Multiple imputation technique will be used to address missing values for primary endpoint in case of percentage of missing data will be ≥ 20%. Multiple imputation it's superior to single imputation in reducing statistical bias by building in random error into the imputation. This prevents under-estimation of the degree of variability in the data, which affects the estimate of the standard error.

The following steps will be used:

- Differences on all key and outcome variables between patients with missing versus non-missing values will be described and tabulated.
- Missing data will be imputed using SAS PROC MI under the assumption that the missing values are missing at random (MAR). This assumption requires that missing values be related to measured covariates, with no unmeasured related covariates.
- Results will be aggregated across the multiply imputed data sets using SAS PROC MIANALYZE.

The multiple imputation model will include the primary outcome as the number of wet nights during the last week on the 4 weeks period after randomisation, randomisation group, average number of wet nights during the run-in period, age and sex. The number of imputation data sets to be created is 100.

15.1.3 Primary Analysis of Primary Variable

The primary objective of this study is to demonstrate if discontinuation of nocturnal use of absorbent pants in children with NE has any impact on the rate of spontaneous resolution of NE, compared with continued use of absorbent pants, over a period of 4 weeks.

The primary effectiveness analysis will be performed for the PAS comparing the 95% CI for the difference between the means of average wet nights at the end of intervention period for the 2 groups with the predefined margin ($\delta = 2/7$). If the CI lies strictly within $[-\delta, +\delta]$, the study hypothesis will be demonstrated. Difference in means and CI will be generated by PROC TTEST for independent groups.

Primary analysis will be also repeated by age groups (4–<6 years and ≥6–8 years).

15.1.4 Sensitivity Analysis of Primary Variable

The sensitivity analysis will be performed as described in Section 15.1.2 in case of observing 20% or more of the missing date for the primary variable. Descriptive statistics for the analysis population will be computed comparing the original values to the imputed values.

15.2 Secondary Analysis

Analysis of secondary endpoints will include, QoL and sleep quality assessed via a set of validated questionnaires for the participants and their parent/carers at each study clinic visit. In particular:

- Paediatric Incontinence Questionnaire
- World Health Organization Quality of Life
- Paediatric Daytime Sleepiness Scale
- Checklist Individual Strength

Additionally, the perception of DryNites® attributes, compared to previously used absorbent products will be evaluated through 2 specific questionnaires designed for this study.

Secondary analysis will be performed on RND set.

15.2.1 Secondary Variables & Derivations

15.2.1.1 PinQ

The PinQ *(*Bower et al. 2006) measures the emotional impact that urinary incontinence has on a child. It consists of 20 urinary incontinence QoL related questions which are graded on a scale of 0–4 (0=No, 1=Hardly ever, 2=Sometimes, 3=Often, 4=All the time) with a total possible score of 80.

Two factors scores cast the items from the children's questionnaires into 2 groups, which could be considered as extrinsic (items 2, 3, 6, 12, 16 and 20) and intrinsic (items 1, 4, 5, 7, 8, 9, 10, 11, 13, 14, 15, 17, 18, 19, 20) impact. Intrinsic items generally related to how the child felt or what they believed, whilst the extrinsic items were more likely to relate to external limitations imposed by urinary symptoms.

The factor score will be obtained as the sum of items included in each factor and the total score will be calculated as the sum of each single non-missing score. Scores will indicate the impact urinary incontinence has on the child's QoL with the higher score indicating a more significant effect.

15.2.1.2 WHOQoL-BREF

The WHOQoL-BREF questionnaire (WHO 1996) assesses the individual's perceptions in the context of their culture and value systems, and their personal goals, standards and concerns. It comprises 26 items, which measure the following broad domains: physical health (items 3, 4, 10, 15, 16, 17 and 18), psychological health (items 5, 6, 7, 11, 19 and 26), social relationships (items 20, 21 and 22), and environment (items 8, 9, 12, 13, 14, 23, 24 and 25). There are also 2 items that are examined separately: item 1 asks about individual overall perception of quality of life and item2 asks about individual overall perception of their health.

Domain scores are scaled in a positive direction (i.e. higher scores denote higher QoL). The scores of items 3 ("To what extent do you feel that physical pain prevents you from doing what you need to do?"), 4 ("How much do you need any medical treatment to function in your daily life?") and 26 ("How often do you have negative feelings such as blue mood, despair, anxiety, depression?"), which are negatively phrased, will be reversed.

The mean score of items within each domain will be used to calculate the domain scores. The mean will be then multiplied by 4 as to be directly comparable with scores derived from the WHOQOL-100. As last steps, the data transformation reported below will be applied to obtain a 0-100 score:

- Domain 1 to 4: (domain score – 4)*100/16;
- Item 1 and 2: (items score – 1)*100/4.

Higher scores denote higher QoL.

Where more than 20% of data is missing from an assessment, the assessment should be discarded. Where an item is missing, the mean of other items in the domain is substituted to the missing item score. Where more than 2 items are missing from the domain, the domain score should not be calculated (except for domain 3 [Social relationships], where the domain should only be calculated if <1 item is missing).

The 3 questions added at the end of the questionnaires will be listed only.

15.2.1.3 PDSS

The PDSS questionnaire (Drake et al. 2003) has been developed to measure daytime sleepiness of middle-school children and examine the relationship between daytime sleepiness and school-related outcomes.

It consists of 8 items assessing daytime sleepiness and rated on a 5-point Likert scale ranging from 4 (Always/ Very often) to 0 (Never); the score of the third item ("Are you usually alert most of the day?") will be reversed to calculate the total score as the sum of single items score. Higher scores

indicate greater daytime sleepiness, and were associated with reduced total sleep time, poorer school achievement, poorer anger control, and frequent illness.

15.2.1.4 CIS

The CIS (Bültmann et al. 2000) is a 20-item fatigue questionnaire for which the person indicates on a 7-point scale to what extent the particular statement applies to him or her and it measures 4 dimensions of fatigue: fatigue severity (items 1, 4, 6, 9, 12, 14, 16, 20), concentration problems (3, 8, 11, 13, 19), reduced motivation (2, 5, 15, 18) and activity (7, 10, 17). Each domain score is calculated as the sum of items included in the domain. The CIS total score can be calculated by adding the 4 dimensions.

15.2.1.5 Absorbent Pants and DryNites® Clinical Trial Questionnaires

The child and parents'/carers' perspectives on their experience with previous absorbent pants/nappies, and on the attributes of DryNites® vs. previously used products will be recorded via 2 specific questionnaires designed for this study and administered at study entry (Absorbent Pants Clinical Trial Questionnaire, about previous products) and at Day 28 ± 7 (DryNites® Clinical Trial Questionnaire).

Each questionnaire includes the following: identification of previous absorbent product (question 1), 2 narrative questions, 11 statements about the absorbent product (responses: Agree, Tend to agree, Neither agree or disagree, Tend to disagree, Disagree). The Absorbent Pants Clinical Trial Questionnaire includes 6 questions on the attributes of the previous absorbent product, responded on a 1-10 scale (with 1= not at all, and 10 being the highest level of appreciation). The DryNites®

Questionnaire includes an overall preference question, responded on a 1-10 scale, and 8 specific questions on preference for DryNites® attributes compared to the previous absorbent product.

15.2.2 Missing Data Methods for Secondary Variables

No reliable methods are proposed to manage missing data in PinQ, PDSS and CIS. Please see Section 15.2.1.2 for instruction on missing management for WHOQoL-BREF.

Total scores and the domain scores (applicable for PinQ and CIS only) will be calculated in case of at least 50%+1 of questions completed and the subscale score will be prorated by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered. The results obtained will be presented along with results obtained without missing substitution.

No missing substitutions will be applicable on Absorbent Pants and DryNites® Clinical Trial Questionnaires.

15.2.3 Analysis of Secondary Variables

15.2.3.1 Analysis of Secondary Variables

Analyses of PinQ, WHOQoL-BREF, PDSS and CIS questionnaires will be provided by group on the Randomised Set.

Frequency distribution and descriptive statistics, when applicable, will be provided by visit for each item of questionnaires, while summary statistics for total scores, domain scores and changes from baseline will be provided as applicable.

The effect size will be also presented as descriptive statistics of ratio between the change from baseline and baseline SD.

The percentage of patients with change from baseline ≥0.5 time the baseline SD will be also provided.

For applicable questionnaires an ANCOVA with baseline PROs value as covariate will be performed. Group comparisons will be performed for the difference in least squares means (LSMean) at Visit 3. The LSMean (standard error [SE]) by group and visit (if applicable), the LSMean difference between groups, along with 95% confidence limits of the group differences and the p-value for the group comparison will be displayed as purely exploratory. For the change from baseline, p-value for the within-group difference will also be displayed as purely exploratory.
The Absorbent Pants Clinical Trial Questionnaire administered at study entry, and the DryNites® Clinical Trial Questionnaire administered at the end of the run-in period, will be analysed descriptively for the Screened Set.

15.3 Exploratory Analysis

The exploratory analysis will include the refresh of the analysis on patient disposition, primary and secondary analysis and adverse events, including the data collected over the extension period.
A repeated measure model will be presented to assess the extension period effects on PinQ, WHOQoL-BREF, PDSS and CIS questionnaires.
Repeated measure model will be handled with mixed effects models using SAS PROC MIXED with an unstructured correlation matrix to model the within-patient errors, unless the model does not converge, in which case the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive covariance structure will be checked. Parameters will be estimated using the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated

using the Kenward-Roger approximation by fitting values from post-randomisation scheduled visits. This likelihood-based approach is tolerant of missing data provided that they are MAR. Missing at random assumes that the missing values are systematically related to other, measured covariates and that no unmeasured related covariates exist.

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set.

16.1 Adverse Events

Adverse Events (AEs) will be coded using the version of MedDRA available at the time of the analysis.

Treatment emergent adverse events (TEAEs) are defined as AEs that first occurred or worsened in severity after the start of screening period and prior to the end of the extension period.

See Appendix 1 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst-case scenario; i.e. treatment emergent.

The AEs that occurred from ICF signature till randomisation will be described separately and presented in a listing.

For each group, numbers and proportion of TEAEs, device-related TEAE and serious TEAEs will be tabulated by SOC and PT along with number of events.

Medical Device Incidents (MDI) not associated with a TEAE will be described separately in a listing.

16.1.1 All TEAEs

Incidence of TEAEs and AEs along with the number of events, will be presented by SOC and PT. AEs occurred more than once within that SOC/ PT will be counted once in the summary tables (at least one occurrence). The SOCs will be presented by alphabetical order, and PTs by descending frequency within each SOC.

16.1.1.1 Severity

Severity is classed as mild/ moderate/ severe (increasing severity). TEAEs with a missing severity will be classified as severe.

16.1.1.2 Relationship to Study Device

Relationship, as indicated by the Investigator, is classed as "unrelated", "unlikely", "possibly", "probably" (increasing severity of relationship). A "related" TEAE is defined as a TEAE with a relationship as "unlikely", "possibly", "probably". TEAEs with a missing relationship will be regarded as related. For related TEAEs summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared together with number of events. In case of less than 5 events, a listing only will be provided.

16.1.2 TEAEs Leading to Discontinuation of Study Device

All TEAEs leading to permanent discontinuation of medical device will be identified by "Action taken with study device" variable collected on the Adverse Events page of the eCRF and completed as "device withdrawn".

For TEAEs leading to discontinuation of study device, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared. In case of less than 5 events occurred, a listing only will be provided.

16.1.3 Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared. In case of less than 5 events occurred, a listing only will be provided.

16.1.4 Adverse Events Leading to Death

The TEAEs leading to death are those events which are recorded as "Fatal" on the Adverse Events page of the eCRF. A summary of TEAEs leading to death by SOC and PT will be prepared. In case of less than 5 events occurred, the events will be identified by the listing of serious adverse events.

16.1.5 Medical Device Incident

Medical Device Incident will be identified by "Is this event considered a Medical Device Incident (MDI)" variable collected on the Adverse Events page of the eCRF and completed as "Yes". A summary of MDI by SOC and PT will be prepared. In case of less than 5 events occurred, the MDI will be listed only.

16.2 Deaths

If any patient dies during the study as recorded on the AE page of the eCRF, the information will be identified by the SAE listing only.

16.3 Laboratory Evaluations

Not applicable.

16.4 Vital Signs

Not applicable.

16.5 Physical Examination

The following summaries will be provided for physical examination data performed at Visit 1 on SCR and RND Set (overall and by age groups):

- Incidence of abnormalities overall (at least one abnormalities);
- Incidence of abnormalities upon external genitalia examination of urethral meatus, overall and for each available pre-specified condition (hypospadias; meatal stenosis; phimosis; labial adhesions, other);
- Incidence of abnormalities upon examination of the lower back overall and for each available pre-specified condition (dimples, hypertrichosis, suspect palpatory finding, other);
- Incidence of abnormalities upon orienting neurological examination and inspection of the feet;
- Incidence of abnormalities upon grasp function of the toes tested for an intact S1-S2-S3 innervation;

17. REFERENCES

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Bültmann U, de Vries M, Beurskens AJ, Bleijenberg G, Vercoulen JH, Kant I. Measurement of prolonged fatigue in the working population: determination of a cut-off point for the checklist individual strength. J Occup Health Psychol. 2000; 5(4): 411-6.

Drake C, Nickel C, Burduvali E, Roth T, Jefferson C, Badia P. The Pediatric Daytime Sleepiness Scale (PDSS): sleep habits and school outcomes in middle-school children. Sleep 2003; 26(4): 455-8.

World Health Organization: WHOQOL-BREF: Introduction, Administration, Scoring and Generic Version of the Assessment—Field Trial Version. Geneva: WHO, 1996

17.1 APPENDIX 1. Partial Date Conventions

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < screening date, then not TEAE If start date >= screening date, and <= End of extension period, then TEAE
	Partial	If start date < screening date, then not TEAE If start date >= screening date, and <= End of extension period, then TEAE
	Missing	If start date < screening date, then not TEAE If start date >= screening date, and <= End of extension period, then TEAE
Partial, but known components show that it cannot be on or after randomisation	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE

START DATE	STOP DATE	ACTION
Partial, could be on or after screening	Known	If stop date < screening date, then not TEAE If stop date >= screening date, and <= End of extension period, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < screening date, then not TEAE If stop date >= screening date, and <= End of extension period, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < screening date, then not TEAE If stop date >= screening date, and <= End of extension period, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < screening date, then not TEAE If stop date >= screening date, and <= End of extension period, then TEAE

START DATE	STOP DATE	ACTION
	Missing	Assumed TEAE

TEAE: Treatment emergent adverse event

Electronic Signature Manifestation

This page is a manifestation of the electronic signature(s) used in compliance with the organization's electronic signature policies and procedures.

Signer Full Name	Meaning of Signature	Date and Time
Sara Colli	Document Approval	11 Feb 2020 08:46:43 UTC
Katerina Chaintarli	Document Approval	11 Feb 2020 09:03:02 UTC
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