Official Title: PRO Solo**:** Patient-Reported Outcomes with the Accu-Chek® Solo micropump system vs. Multiple Daily Injection Therapy vs. mylife OmniPod® in Patients with Type 1 Diabetes

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STATISTICAL ANALYSIS PLAN

Study Protocol RD002718

PRO Solo: Patient-Reported Outcomes with the Accu-Chek® Solo micropump system vs. Multiple Daily Injection Therapy vs. mylife OmniPod® in Patients with Type 1 Diabetes

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Signatures

I confirm that this Statistical Analysis Plan accurately describes the planned statistical analyses to the best of my knowledge and was finalized before database closure.

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List of Abbreviations and Key Terms

AE	Adverse Events
ANCOVA	Analysis of Covariance
BG	Blood Glucose
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CSII	Continuous Subcutaneous Insulin Infusion
DRM	Data Review Meeting
DTQ	Diabetes Technology Questionnaire
eCRF	electronic Case Report Form
FAS	Full Analysis Population
HbA_{1c}	Glycated Hemoglobin
LOCF	Last Observation Carried Forward
MDI	Multiple Daily Injections
MedDRA	Medical Dictionary for Regulatory Activities
PAID-5	Problem Areas in Diabetes Scale Questionnaire
PP	Per Protocol Population
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SP	Safety Population
SFTP	Secure File Transfer Protocol
SMBG	Self-Monitoring of Blood Glucose
TBD	Total Daily Basal Insulin Dose
TDD	Total Daily Insulin Dose

1. Introduction

This statistical analysis plan (SAP) is a detailed elaboration of the statistical analyses described in the study protocol RD002718, Version 4.0, dated 21.Jun.2018, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. The SAP is to be finalized and signed prior to database closure.

2. Study Design and Objectives

2.1. Objective

The aim of this study is to compare treatment satisfaction with the Accu-Chek® Solo micropump system versus MDI and versus mylife™ OmniPod® assessed by Diabetes Technology Questionnaire (DTQ).

Additionally, the following parameters will be compared

- Psychological parameters that describe or affect therapy:
    - Diabetes-related Emotional Distress assessed by the Problem Areas in Diabetes questionnaire (PAID-5).
    - Device satisfaction
    - Device and Treatment Preference
- Physical parameters that describe therapy changes or success:
    - HbA_{1c}
    - Change in weight and Body Mass Index (BMI)
    - Glycemic variability
- Therapy parameters that describe therapy changes or may affect the results
    - Indication for commencement of CSII
    - Type of insulin used
    - Total daily insulin dose (TDD)

- Total daily basal insulin dose (TBD)
- Average number of SMBGs per day
- Frequency of hypoglycemic events
- Frequency of hyperglycemia

2.2. Study Design

This study is conducted as a prospective, multinational, multicenter, three-arm study where adults with type 1 diabetes will be enrolled in approximately 20 sites.

A total of 180 subjects will be randomly allocated in a 1:1:1 ratio to the three treatment groups.

Due to the character of the used devices, no blinding procedure will be utilized.

2.3. Study Phases

The study consists of two phases. During phase 1, the parallel phase, all subjects use for 26 weeks a device according to the treatment group they have been randomized to. During phase 2, all subjects use the Accu-Chek® Solo micropump system for 13 additional weeks.

2.4. Treatment Groups

Group A: Continuous subcutaneous insulin infusion (CSII) with the Accu-Chek® Solo micro-pump system for 39 weeks (26+13).

Group B: Multiple daily injections (MDI) for 26 weeks plus 13 weeks with the Accu-Chek® Solo micropump system.

Group C: Continuous subcutaneous insulin infusion (CSII) with the mylife™ OmniPod® ther-apy system for 26 weeks plus 13 weeks with the Accu-Chek® Solo micropump system.

2.5. Primary efficacy endpoints

The primary goal of the study is to assess, if treatment satisfaction in the Accu-Chek® Solo group (Group A) increases in comparison to the group using MDI (Group B) and to the mylife™ OmniPod® group (Group C). Change in treatment satisfaction will be assessed by Part 1, “Im-pact and Satisfaction” of the Diabetes Technology Questionnaire (DTQ). This question-naire

consists of two parts of identical questions, the status part (“Is this a problem now?”) and the change part (“How has it changed compared to your treatment before the study?”). For the current study, the change part (“How has it changed compared to your treatment before the study?”) will be used as primary variable with the status part as covariate.

The status part can be answered with a rating between 1 (very much) and 5 (not at all), the change part with a rating between 1 (much worse) and 5 (much better). For both parts, the sum of all individual answer scores will be used for analysis.

The change score as dependent variable will be analyzed with an Analysis of Covariance (ANCOVA) with group as independent variable and the status (“Is this a problem now?”) answers of the DTQ assessed at Visit 1 (V1) and the site as covariates.

2.6. Hypothesis Testing

As described above, objective of this study is the assessment of treatment satisfaction in patients with type 1 diabetes comparing Accu-Chek® Solo therapy versus MDI and mylife™ OmniPod, an established patch pump. The following hypotheses will be tested

First Null hypothesis: There is no difference in treatment satisfaction between Accu-Chek® Solo and MDI.

First Alternative hypothesis: Treatment satisfaction is higher with Accu-Chek® Solo than with MDI.

Second Null hypothesis: There is no difference in treatment satisfaction between Accu-Chek® Solo and mylife™ OmniPod.

Second Alternative hypothesis: Treatment satisfaction is higher with Accu-Chek® Solo than with mylife™ OmniPod.

2.7. Hierarchical Testing Procedure

The comparisons between the Accu-Chek® Solo group and MDI and between the Accu-Chek® Solo group and the mylife™ OmniPod group will be performed hierarchically. Only if the comparison between the Accu-Chek® Solo and the MDI group will show a statistically significant difference, the comparison between the Accu-Chek® Solo and the mylife™ OmniPod® group will also be performed.

2.8. Sample Size Calculation

Sample size calculation is based on the expected difference and variability in the DTQ change score between the Accu-Chek® Solo and the MDI group. An anticipated mean score of 90 in the MDI group corresponding to no change and of 110 in the Solo group and a standard deviation of 30 is used for sample size calculation.

A sample size of 49 subjects per group will have a 90% power to detect a significant difference at a two-sided alpha level of 0.05. To adjust for a maximum drop-out rate of up to 18%, 60 subjects will be enrolled in every treatment arm.

To allow for comparison between the Accu-Chek® Solo and the mylife™ OmniPod, the same number of subjects as in groups A and B will be enrolled in group C. No assumptions on the difference in change of treatment satisfaction between the Accu-Chek® Solo and in the mylife™ OmniPod groups are made and thus, sample size is not adjusted for this comparison. Since testing of the first and the second Null hypothesis will be performed, using the hierarchical procedure described above, no multiplicity correction and thus no sample size adjustment is necessary.

Subjects that withdraw form this study will not be replaced.

2.9. Study Duration and Phases

The total duration of the study is 39 weeks plus one additional week for a follow-up call. These 39 weeks are split into two major phases. A parallel phase (26 weeks), for which subjects are randomly assigned to one of three treatment groups and a second phase (13 weeks), during which all subjects will use the Accu-Chek® Solo micropump. Subjects in treatment arm A will keep their study devices while subjects in treatment arms B and C will receive an Accu-Chek® Solo micropump system and will be trained on this device.

The following visit schedule is defined for this study.

- Visit 1 – Screening (-14 to 0 days)
- Visit 2 – Baseline (day 1)
- Visit 3 – Middle of parallel phase (week 13)
- Visit 4 – End of parallel phase (week 26)

- Visit 5 - Final Visit (week 39)
- Follow-up call (week 40)

2.10. Populations for Analysis

Due to the design of the study with a parallel phase between visits 1 and 4 and a one-armed phase in which all subjects will use the Accu-Chek® Solo micropump system, analysis will distinguish between these phases. Wherever appropriate, the treatment arm, to which a subject is randomized, will be denoted as “arm”, the current treatment as “trt” in listings and tables. E.g., a subject randomized to treatment arm B (MDI) will therefore have the analysis assignments B for both, arm and trt between visits 1 and 4, while the corresponding assignments will be B as arm and A as trt between visits 4 and 5.

The following populations are defined for analysis:

- The safety population (SP) is defined as all enrolled patients with data documented at at least one of the visits 1 to 5.
- The full analysis population (FAS) will follow the intention to treat principle, i.e., all subjects will be analyzed according to the treatment arm they are randomized to..
- The per-protocol (PP) population will be defined on a per visit basis. For a given visit, it will include all subjects that will have completed this visit and have no severe protocol deviations.

2.11. Interim Analysis

An interim analysis will be conducted when all patients have either passed visit 4 (End of parallel phase) or have withdrawn from the study, i.e. when all data for performing the primary analysis and the majority of the secondary analyses will be available. No changes to the study protocol will be implemented due to the results of this interim analysis. Nevertheless, all analyses will be repeated after database closure and results based on fully cleaned data will be reported in the CSR.

3. Data Handling

3.1. Patient and Site Identification

Sites are encoded with a two-digit number (with leading zeros) with numbers between [redacted] and [redacted] code for German sites, numbers between [redacted] and [redacted] code for Austrian sites, numbers between [redacted] and [redacted] for UK site and numbers between [redacted] and [redacted] are reserved for Polish sites.

Within each site, subjects are encoded with a three-digit number (also with leading zeros), starting with [redacted].

Complete patient IDs consist of site-id, followed by a dash, followed by the patient number within the site. An example patient ID would therefore be "[redacted]".

3.2. Data conversion

In cases where the eCRF allows entering data in different units, respective data will be converted and the converted form will be used for analysis and for reporting.

- HbA1c will be converted to "%"
- BG values will be converted to mg/dL
- Length will be converted to "cm"
- Weight will be converted to "kg"

3.3. Schedule of Assessments relevant for Analysis

Visits / Procedure	Visit 1 Screening	Visit 2 Baseline	Visit 3	Visit 4	Visit 5	Phone Follow up[1]
Time point		day 1	week 13	week 26	week 39	
Time window (+/- days)		0 to +14 days to Visit 1	±14 days	±14 days	±14 days	2-5 days >Visit 5
Informed consent	X[2]					
Eligibility check (inclusion/exclusion criteria)	X					
Pregnancy test (ß-HCG urine)[3]	X	X[9]	X[9]	X[9]	X[9]	
HbA_{1c} in central lab	X[4]	X	X	X	X	

Procedure \ Visits	Visit 1 Screening	Visit 2 Baseline	Visit 3	Visit 4	Visit 5	Phone Follow up[1]
Demographic data and other Baseline data	X[5]					
Diabetes & diabetes treatment history	X	X[6]				
Diabetes medication	X	X[6]	X[6]	X[6]	X[6]	
Diabetes-associated diseases and treatment	X	X[6]	X[6]	X[6]	X[6]	
Other diseases and medications	X	X[6]	X[6]	X[6]	X[6]	
Hypoglycemic events (severe, mild)		X	X	X	X	
Time of absence from work or school		X	X	X	X	
Height & weight		X	X[7]	X[7]	X[7]	
Skin reactions		X	X	X	X	
Subject questionnaires	X		X	X	X	
Randomization	X					
Distribution of devices and other study material		X	X	X		
Pump training		X[8]		X[10]		
Carbohydrate Counting Training		X				
Device data download			X	X	X	
A(D)Es/SA(D)Es		X	X	X	X	X[1]
Malfunctions			X	X	X	
Collect study devices and other study material				X	X	

1 If ongoing A(D)E/SA(D)E at visit 5
2 Written informed consent must be obtained prior to any study related procedure
3 If applicable
4 Performed in local lab
5 Year of birth, gender, race; handedness, highest level of education, employment status, family status
6 If any changes
7 Weight only
8 For group A and C
9 if applicable by local law (e.g., in Austria)
10 For group B and C

3.4. Handling of Withdrawals and other Missing Data

3.4.1. Handling of missing data affecting the primary endpoint

As described in section 2.10, all randomized subjects will be part of the FAS group and thus be utilized for primary analysis. The status part (“Is this a problem now?”) of the DTQ will be completed by the subject before randomization. Thus it is ensured that status data is available for all subjects and that no bias is introduced by a potential preference of subjects for a particular group, which may result in a withdrawal of individual subjects right after randomization.

For subjects that answered the DTQ during Visit 4, these answers will be used for the primary analysis.

The following steps will be performed to handle missing change data:

In case of withdrawal, subjects will be asked to answer the DTQ questionnaire during the End of Study visit.

If it will not be possible to get questionnaire results at the End of Study visit but questionnaire results are available for week 13 (visit 3), these results will be used, i.e., a LOCF procedure will be applied.

If there are no results for week 13, e.g., because a subject withdrew before week 13, a value of 3 (“Same”) will be imputed as the answer to every individual question. This will result in a total score of 90, which corresponds to the expected mean result for the MDI group and thus represents a conservative imputation (the anticipated mean score for the Accu-Chek® Solo group is 110).

Technically, data acquired during the End of Study visit will be part of the Visit 5 eCRF variables. Consequently, the LOCF procedures described above will copy data from there. Should the End of Study data be not available, the respective data of the available last visit will be used.

3.4.2. Incomplete DTQ questionnaires

The handling of questionnaires that are missing completely is described in the previous section. It is however also possible, that questionnaires are only partially completed. Incomplete DTQ questionnaires will be handled according to the questionnaire’s “Scoring Instructions”. As

described above, a score between 1 and 5 is assigned to each possible answer, resulting in a maximum score of 150 if all answers are provided. If at least 22 questions have been answered, the sum score will be divided by the number of answered questions and multiplied by 30 to get a total sum. If 21 or less questions have been answered, the questionnaire will be treated as missing and handled according to the previous section.

3.4.3. Handling of empty fields in the diabetes medication forms

Investigators are only supposed to enter insulin doses if they differ from 0. Consequently, empty fields in the insulin dose fields are considered normal and will simply be imputed with 0 for analysis. Insulin to carbohydrate ratios will be handled similarly. Investigators usually only enter data if they differ from those entered previously. In order to account for this fact, empty values in these forms will be imputed with the value from the previous timepoint. This applies for the variables “Units”, “Grams”, and “mg/dl” respectively “mmol/l” in the diabetes medication forms.

3.4.4. Handling of other missing data

Missing values for scores other than the primary endpoint and those described in the previous section will be imputed using a LOCF approach, where applicable. In case of missing device data, where a LOCF approach would be meaningless, e.g., BG values or applied Insulin bolus and basal amounts, statistics will be calculated based on available information.

3.5. Coding Systems and Conventions

3.5.1. Technical Aspects and Coding Conventions

Tables, figures, and listings will be provided in the same PDF document. The PDF will have a DIN A4 format and include a corresponding table of content preceding the content of the file. Page orientation will be changed between portrait and landscape on a page-to-page basis depending on optimum placement.

3.5.2. Date Coding and Day Numbering

The format for presentation of date variables will be DDMMMYYYY. The format for presentation of time variables will be hh.mm.

Partially entered dates (e.g., only year or only year and month) will be completed, if they are necessary for the calculation of durations required for the statistical analysis. Deviations from this procedure will be reported and justified in the clinical investigation report.

All assessment dates will be related to the date of V2. The study day will be calculated as described below:

Study day = Date of visit – Date of V2 + 1.

3.5.3. Incomplete Dates

For a limited number of fields, the eCRF allows to enter incomplete dates in cases if the exact date is not known to the subject or the investigator, e.g., the date when diabetes was first diagnosed. For analysis, dates where only the year is known/given, July 1 will be used. If the month but not the day is known, 15 will be inserted as day. E.g., “2005” will be replaced by “01-Jul-2005” and “Sep-2010” will be replaced by “15-Sep-2010.

3.5.4. Special Handling of Visit 4

3.5.4.1. Safety Events at Visit 4

Subjects randomized to treatment arm B (MDI) and C (OmniPod) will receive the Accu-Chek® Solo micropump system only at Visit 4. As a consequence, safety events (AEs and SAEs) cannot be assigned to either the randomized treatment or the Accu-Chek® Solo micropump system based on the date of the event alone. If an assignment to a device will be available from the investigator and confirmed by Safety, it will be used for the analysis. Otherwise, the event will be assigned to the Accu-Chek® Solo micropump system to guarantee conservative results.

3.5.4.2. Device Use Time

Subjects will receive their study device (Accu-Chek® Solo micropump system, MDI, or OmniPod®) at Visit 2. Additionally, as described above, study subjects randomized to arms B and C will utilize two devices at the day of Visit 4. Consequently, for all analyses utilizing the number of days a given device is used, use time will be calculated starting at Visit 2. For subjects randomized to treatment arms B (MDI) and C (OmniPod), the day of Visit 4 will be counted for

both, that is for the randomized device and for the Accu-Chek® Solo micropump system. For subjects in treatment group A, the Visit 4 day will however only be counted once.

3.5.5. Coding of Adverse Events and Medical History

Adverse event and medical history terms are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology version in effect at the time the database is closed. MedDRA term level (LLT, PT, and SOC) are utilized depending on the particular needs of a given analysis. What term level will be used will be defined with the analysis definition.

Certain medical conditions, e.g hyperglycaemia and ketonuria have completely different MedDRA codings, however they may be caused by identical reasons, e.g., lack of insulin. Medical Safety may therefore request pooling of such events. If this is applied, it will be explained as part of the respective analysis.

3.5.6. Coding of medications

Previous and concomitant medications are coded using the WHODrug dictionary. A semi-automatic coder built into the Marvin eCRF system is used for coding and the results will be extracted to SAS files for further analysis.

4. Variables for Analysis

In this section, data sources whose origin or initial preparation is not obvious are explained. Details about the actual analysis are provided in section 6.

Wherever text in languages other than English has been entered in sections relevant for analysis (e.g., in questionnaires), these texts will be translated into English and the English translation will be provided in listings etc.

4.1. Data for Primary Analysis

Change in treatment satisfaction is assessed by the answers to the change part questions (“How has it changed compared to your treatment before the study?”) of the Technology Questionnaire (DTQ). Each of these answers has a score between 1 (much worse) and 5 (much better). The sum of all 30 individual answers will be calculated for each subject/visit combination and will be used for analysis. Missing values will be imputed as described in section 3.4.1.

Answers entered in the status part (“Is this a problem now?”) of this questionnaire at visit 1 will be used as covariate.

4.2. Data for other Analyses

4.2.1. Questionnaires

4.2.1.1. DTQ Questionnaire Change and Status Parts

As described section 4.1, the DTQ questionnaire consists of a change part in which subjects are asked for changes in their treatment satisfaction and of a status part, in which they are asked for their current rating. The change score (with V1 status score as covariate) will be used to analyze change compared to pre study status, while the differences between V4 and V5 (e.g., for subjects changing from MDI or the mylife™ OmniPod® therapy system to the Accu-Chek® Solo micropump system) will be calculated based on the respective “now” scores.

4.2.1.2. DTQ Questionnaire Part 2 (User Friendliness)

Part 2 of the DTQ questionnaire consists of individual sections with 9 questions each for blood glucose meters, insulin pumps, and CMG devices. Main focus of part 2 questions is user-friendliness. Individual scores range from 1 (Terrible) to 5 (Excellent). Thus the resulting sum score ranges between 9 and 45 for each type of device. For all sections, higher scores denote a better user-friendliness.

Missing individual answers will be handled in accordance to the described handling for part 1. If three or less answers are missing in a given section, the total section score will be calculated as nine times the mean of the all answers provided. If more answers are missing, the entire section will be considered as missing and the LOCF procedure defined for DTQ will be applied.

4.2.1.3. PAID-5 Questionnaire (Emotional Distress)

The PAID-5 questionnaire consists of 5 questions with answers ranging from 0 (Not a problem) to 4 (Serious problem). The total score will be calculated as the sum of the individual questions, resulting in a number between 0 and 20 where lower scores are better.

Missing individual answers will be treated in accordance to the procedure described for DTQ. If one answer is missing, the mean of the answers provided will be used to calculate the total

sum, otherwise the questionnaire will be treated as missing and the LOCF procedure will be applied.

4.2.1.4. Roche Questionnaire

The Roche questionnaire consists of 28 questions covering six areas, namely “Diabetes manager” (5 questions), “Pump” (4 questions), “Changeover” (4 questions), “Adhesive pad” (3 questions), “Overall system” (7 questions), and “Miscellaneous” (5 questions). Answers in the first five of these areas range from 4 (Agree) to 0 (Disagree) where higher scores are better. The “Miscellaneous” area consists of 5 free text answers. Total area scores from the first five areas will be calculated as the sum of scores in this area while the total questionnaire score will be calculated as the sum of all scores of the questionnaire. The total score will therefore be between 0 and 92. The free-text answers in the “Miscellaneous” section will only be listed but not further analyzed.

Missing individual answers will be treated in accordance to the procedure described for the DTQ. If more than one answer is missing for an individual section, this section will be treated as missing. For completely missing questionnaires, the LOCF procedure described earlier will be applied. Otherwise, sum scores will be calculated as described for DTQ.

4.2.1.5. Examination of Insertion Sites

Subjects are asked to assess five different properties describing potential problems at the pump insertion site, namely “itching”, “redness”, “swelling”, “heat”, and “pain”. Each of these questions can be answered with one of four alternatives, “None”, “Minor”, “Moderate”, and “Severe”.

4.2.2. Blood Glucose Data

Study subjects utilize various alternatives to collect blood glucose data during this study. The main distinctive feature is, whether collection is based on spot (BGM) or continuous (CGM) measuring. Differences within these two major classes are not of interest for this study.

Certain analyses are only meaningful for data originating from one of the two technologies, e.g., average number of SMBGs per day, while others may be utilized for both. The analysis will consider this by analyzing BGM and CGM data separately. Details are described in section 6.8.4.

4.2.3. Insulin Dosing

Insulin dosing information, i.e. insulin types, basal and bolus rates, and total insulin consumption will be taken from the entries in the eCRF. For pump users, more precise dosing information will additionally be extracted from the uploaded device data where possible. For analysis purposes, data taken from the eCRF and data acquired from device uploads will be used and listed separately.

5. Data Review

Before database closure, a Data Review Meeting (DRM) will be performed. In case there are open questions/discrepancies for a subject that cannot be solved via internal data review, a list with a description of the open issues will be evaluated case-by-case.

6. Statistical Analyses and Representation of Results

6.1. General

All analyses will be performed by SAS (Statistical Analysis Software), version 9.4. The analysis will be executed and checked according to SOP 04.04.50 V1.0 "Statistical Analysis of Clinical Trials".

Wherever appropriate, e.g., for demographics, descriptive analyses for the different treatment groups will be tabulated next to each other in the same row to allow for visual comparison. No statistical testing will however be performed unless specified explicitly in this document.

6.2. Analysis Populations

Primary population for all except safety relevant analyses is the FAS as described in section 2.10. Additionally, for completeness, the primary analysis will also be performed on the per protocol population. All safety relevant analyses will be performed on the SP.

6.2.1. Distinction of Study Phases

As already described in 2.10, the study consists of two phases. To allow for easy distinction e.g., in listings, two variables, Arm and Trt are assigned to data acquired from each subject depending on the study phase and device assignment during data assessment.

Arm Variable	Phase 1 (V1 - V4)		Phase 2 (V4 – V5)	
	Device	Trt Variable	Device	Trt Variable
A	Solo	A	Solo	A
B	MDI	B	Solo	A
C	OmniPod	C	Solo	A

Descriptive statistics for V5 data will both be calculated separately for each study arm and overall for all subjects.

6.3. Statistical Analysis Methods

The default summary statistics for continuous variables will be the number of observations (n), mean, standard deviation (SD), median, first and third quartile (Q1 and Q3), minimum (min), and maximum (max).

Apart from DTQ with its explicit change score, change from baseline will everywhere be evaluated by subtracting the baseline value from the value observed at the visit of interest. Wherever change scores will be listed or tabulated, the same statistics will also be presented for the baseline and visit values.

All summary statistics will be presented to one more decimal place than the raw value, except for the minimum and maximum values that will be presented with the same decimal precision as the raw value. Percentage values will be presented to one decimal place. Thus, percentages lower than 100% will be displayed as “XX.X”. E.g., a proportion of 0.655 will be presented as 65.5% where percent scores are given.

Percentages will be calculated using a denominator of all patients in a specified population or treatment group. The denominator will be specified in a footnote to the tables for clarification if necessary.

For qualitative variables, in general, the number (n) and percentage (%) of patients with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a “Missing” category.

6.4. Presentation and Naming of Tables, Figures, and Listings

Tables, figures, and listings will utilize a continuous numbering. First, tables starting with “Table 1”, then Figures starting with “Figure 1” and then listings. The orientation of the document will switch between portrait and landscape depending on space requirements. If a given table or listing does not fit on a page horizontally, the characters “a”, “b”, etc. will be added to the name and extra columns will be put into additional outputs, e.g., “Table 5a”, “Table 5b”, etc.

6.5. Interim Analysis

An interim analysis will be conducted when all patients have either passed visit 4 (End of parallel phase) or withdrawn from the study, i.e. when all data for performing the primary analysis and the majority of the secondary analyses are available This will however be no typical interim analysis with possible adjustment of sample size etc. In this study, no changes on the study protocol nor on the study conduct will be made as a consequence of the results of this interim analysis.

6.6. Analysis of Primary Endpoint DTQ

The primary endpoint of this study is the change in DTQ part 1 as described in 2.5. A hierarchical procedure as described in section 2.7 will be applied. The comparison between Accu-Chek® Solo and mylife™ OmniPod® will only be performed, if the Null Hypothesis of no difference between Accu-Chek® Solo and MDI can be rejected

The comparisons will be performed using an ANCOVA with the DTQ score as dependent variable and treatment arm, baseline DTQ score, and site as covariates. SAS proc GLM will be used for the analysis.

6.7. Analyses of secondary endpoints for static variables

6.7.1. Disposition

Disposition of subjects will be presented by means of:

- Enrolled subjects: All subjects having signed the Subject Informed Consent Form
- Screening failures: Subjects failing one or more inclusion or exclusion criteria
- Randomized subjects
- Withdrawn subjects:

Except for the number of screened subjects, percentages will be provided based on the number of eligible subjects in the respective group of interest. For screening failures, only those inclusion or exclusion criteria will be listed, that were decisive for the failure. For withdrawn subjects, the completion status and the reason for discontinuation will be listed.

6.7.2. Demographics

The following demographic variables will be listed by subject and tabulated by treatment arm

- Sex
- Race
- Age
- Highest level of education
- Handedness
- Marital status
- Current employment

6.7.3. Baseline Characteristics

The following characteristics will be collected at screening and/or baseline visit and will be listed by subject and tabulated by treatment arm:

- Height
- Weight
- BMI

6.7.4. Diabetes History

The following diabetes history related properties will be listed by subject and tabulated by treatment arm.

- Duration of Diabetes
- Diabetes therapy at screening
- Start of diabetes therapy at screening
- Has CGM ever been used
- CGM use (weeks) during last 12 month
- Average daily SMBG frequency during last 3 months
- Previous use of a bolus calculator
- Type of basal insulin
- Type of bolus insulin

6.8. Secondary Endpoints Analyzed by Visit

The following secondary endpoints will be analyzed by study arm and visit. Additionally, since subjects in treatment arms B and C will be switched to Solo micropump treatment after Visit 4, within treatment arm analyses will also be performed where applicable, i.e. analysis will be performed on Visit 4 versus Visit 5 data within each of these two study arms and for completeness, also for arm A.

6.8.1. Questionnaires

Questionnaire results will be analyzed as described in sections 4.1 and 4.2.1.

Wherever not specified explicitly, the following comparisons will be listed by subjects for each questionnaire and also be tabulated by treatment.

- Scores at V1, V3, V4, and V5
- Score difference between V1 and V4

- Score difference between V4 and V5
- Score difference between V1 and V5

6.8.1.1. DTQ

For DTQ both the change scores and the status scores will be analyzed. For the change scores, the same ANCOVA as for the primary analysis will be used. All other comparisons will be analyzed using t-tests.

Difference scores as described in section 6.8.1 will be performed both on the “now” scores and on the “change” scores, even though the latter ones already reflect differences/changes.

6.8.1.2. HbA1c laboratory value

Difference of HbA1c between V4 and V2

Diff HbA1c = HbA1c(V4) – HbA1c(V2)

will be tested hierarchically as described in section 2.7. An Analysis of Covariance (ANCOVA) with HbA1c difference as independent variable and the HbA1c values at V2 and the site as covariates will be utilized.

Additionally, HbA1c values at all visits and the differences between the value obtained at a given visit and the value obtained at V2 will be listed and tabulated by treatment.

6.8.1.3. Impact of Solo Device Version

The device version used the majority of time during the last two weeks before completion of a given questionnaire will be listed for each subject using the Accu-Chek® Solo micropump and tabulated by version and visit.

6.8.1.4. Examination of Insertion Sites

Answers to the “examination of insertion site” questions will be listed by visit and question and will be tabulated by treatment group and visit.

6.8.2. Diabetes Medication Information

The following diabetes related characteristics will be listed by subject and visit, and tabulated by treatment. For a given visit, always the information from the last change before that visit will be utilized in order to tabulate and list the status at this visit, not the changes.

Additionally, differences between baseline values and V4, between V4 and V5, and between baseline and V5 will be tabulated.

The summary tables for medical history of diabetes will show absolute and relative frequencies for

- Basal insulin used
- Bolus insulin used
- as well as the continuous variable statistics as defined in section 0 for the following variables
- Basal and Bolus doses
- Bolus count

The following information will be listed for each patient and each timepoint specified by the patient

- Insulin sensitivity, glucose target range, carbohydrate factor and the according time range
- Type of basal insulin
- Type of bolus insulin
- Insulin-to-carbohydrate ratio

6.8.3. Diabetes and Concomitant Medication

Previous and concomitant medications (separated for diabetes and for other indications) will be tabulated by study arm and listed by subject.

6.8.4. Blood Glucose Data

As described in section 4.2.2, blood glucose data originating from spot measurement and from CGM differ substantially in their evaluable properties. Some analyses are only meaningful for subjects performing spot measurement, some only for subjects utilizing CGM and some for both. And for subjects utilizing both, the results from some analyses may at least be questionable, even though they are possible. The frequency of spot measurements may for example be misleading if a subject is using both spot and CGM measuring, simply because there is no need for frequent spot measurements if subjects use a CGM data and BGM frequency may thus be biased for these subjects.

Data will be listed and tabulated by study arm and visit. Additionally, differences between V4 and V5 will also be tabulated. Tabulation will follow the description in section 0. Because there are marginal but nevertheless important differences in the analysis of BG and data resulting from spot and CGM measurements, the analysis is described in detail in sections 6.8.4.1 and 6.8.4.2

6.8.4.1. Subjects with BG data only

The following properties will be analyzed.

- Frequency of BG measurements
- Fraction of measurements in the following ranges
    - < 54 mg/dL
    - >= 54 mg/dL and < 70 mg/dL
    - >= 70 mg/dL and <= 180 mg/dL
    - > 180 mg/dL and < 250 mg/dL
    - > 250 mg/DL
- Additionally, the fraction of measurements in the following ranges will be tabulated for each treatment group.
    - < 70 mg/dL
    - >= 70 mg/dL and < 140 mg/dL

- > 140 mg/dL

6.8.4.2. Subjects with CGM data

For subjects with CGM-data, the following properties will be analyzed

- Fraction of measurements in the following ranges
  - < 54 mg/dL
  - >= 54 mg/dL and < 70 mg/dL
  - >= 70 mg/dL and <= 180 mg/dL
  - > 180 mg/dL and < 250 mg/dL
  - > 250 mg/DL
- Additionally, the fraction of measurements in the following ranges will be tabulated for each treatment group.
  - < 70 mg/dL
  - >= 70 mg/dL and < 140 mg/dL
  - > 140 mg/dL
- Glycemic variability will be analyzed and the following statistics will be tabulated
  - standard deviation (SD)
  - coefficient of variation (CV),

6.8.5. Insulin Dosing

Insulin dosing information will be tabulated by treatment and visit. The information extracted from the eCRF and that taken from device uploads (only available for pump users) will be tabulated separately.

Data extracted from the pumps will be limited to two weeks (14 days) prior each visit in order to guarantee a stable status.

Descriptive statistics for the following properties will be tabulated.

- Average basal insulin dose
- Average bolus insulin dose
- Average daily bolus count

For each of these three properties, the changes between doses respectively counts reported as pre study values and those at a given visit will be reported both absolute and relative.

6.9. Therapy Parameters

The following event frequencies will be listed for each individual subject and will also be tabulated by treatment group and visit. Additionally, event frequency differences between V4 and V5 will be tabulated. Tabulations will be performed both based on the number of affected subjects and on the total wear time of the three study devices during the analyzed period.

- Hyperglycemia and related events (e.g., Ketosis or Ketoacidosis) likely caused by insulin underdosing
- Hypoglycemia
- Hospitalizations

6.10. Diabetes Associated and Not Diabetes related Diseases

Both diabetes associated and non-diabetes related diseases will be listed by subject.

6.11. Additional analyses

It will be tested, whether there is a bias in the fraction of subjects withdrawing from the different treatment arms using the Fisher test.

6.12. Evaluation of Safety Variables

The safety analysis will be based on the SP and on the device, a subject is using at the time, when a safety event occurs. Since all subjects in treatment arms B and C will receive an Accu-Chek® Solo micropump system at Visit 4 (week 26) and will use it until the end of the study, AEs and SAEs occurring at or after Visit 4 will be attributed to the Accu-Chek® Solo micropump

system. Distinction will be handled and documented according to the description in section 6.2.1.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries of incidence rates of overall AEs and of individual AEs by MedDRA system Organ Class and Preferred Term will be prepared. Furthermore, summaries will be tabulated for all AEs, AEs by maximum severity, AEs by strongest causality to study device.

Summaries will include number of events, number of subjects affected, the percentages of all subjects for a given treatment, and the events per year of use for a given device.

Defective devices will be tabulated and listed by device type and treatment arm.

Deaths, SAEs and AEs leading to withdrawal will be listed separately.

Episodes (numbers) of the following AEs will be summarized:

- Symptomatic hypoglycemia
- Severe hypoglycemia (SAEs)
- Diabetic Ketoacidosis (SAEs)

The following ADEs are of particular interest:

- ADEs leading to replacement of device.

Incidence rates of all ADEs and of these ADEs and AEs of special interest (as captured on the AE Form in the eCRF) per 100 patient years will be calculated together with exact two-sided 95% CIs assuming that the number of special AEs observed in the study is Poisson distributed.

6.13. Special Analytical Issues

6.13.1. Treatment of incomplete or unmonitored data due to Covid-19 pandemic risk mitigation

The Covid-19 pandemic during the final phase of this study may impact data collection in two different ways. Firstly, in order to avoid the risk of infection at the study sites, some of the subjects did not come to the site in person for the final study visit (V5); this visit was then

performed as a phone-call visit (virtual visit). And secondly, monitoring of some subject data was not possible due to unavailability of site staff.

Neither of these restrictions or changes has any impact on the primary study results, i.e., on analysis of the DTQ.

However the following data from V5 are expected to be missing for those subjects that completed V5 virtually: weight, HbA1c, pregnancy test, skin reaction assessment, device data upload, return of study material.

Missing data will be handled according to the description in section 3.4; no specific analysis pertaining to virtual visits will be performed.

The lack of monitoring however may result in wrong or missing entries in the eCRF. The monitoring status of all variables used for analyses will therefore be extracted from the eCRF and all variables, that have not been monitored, will be displayed underlined in all listings.

Additionally, all descriptive statistics and statistical tests based on data, that include data not monitored will be performed twice. Firstly, using the data as entered in the eCRF and secondly based on data generated by removing the data, that has not been monitored, and replacing it according to the missing value treatment described in section 3.4.

Differences in the statistics obtained using these two different approaches will illustrate the potential impact the data not monitored may have on study results.

6.13.2. Examination of Subgroups

The analysis of all variables will be repeated for all defined subject populations. No explicit additional subgroup analysis will be performed. Different results in the various populations will not be compared explicitly but only mentioned in the report where appropriate.

6.14. Quality assurance

All statistical programs employed in the analysis and reporting of the data will be validated according to the standard operating procedures (SOP 04.04.50 V1) and results will be checked for plausibility.