Statistical Analysis Plan for: Companion protocol for the ^{13}C-Methacetin Breath Test (MBT) for use in Bristol-Myers Squibb phase 2b studies for BMS-986036 (PEG-FGF21), under Protocols MB130-068 and MB130-069

SAP for Protocol No. BMS-EX-0118

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1.0	May 05, 2021	Gil Guggenheim	Initial Release

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1 ABBREVIATIONS

AE - Adverse Event
cDOB - Cumulative Delta over Baseline
CI - Confidence Interval
CL - Confidence Limits
CO_2 - Carbon dioxide
cPDRxx - Cumulative Percentage Dose Recovery at xx minutes from ingestion
CRF - Case Report Form
CSR - Clinical Study Report
CTP - Child-Turcotte-Pugh (score)
DOB - Delta over Baseline
DXA - Dual-Energy X-Ray Absorptiometry
EA - Efficacy Analysis (set)
eCRF - Electronic Case Report Form
GCP - Good Clinical Practice
HCC - Hepatocellular Carcinoma
HE - Hepatic Encephalopathy
HR - Hazard Ratio
IRT - Interactive Response Technology
ITT - Intent to treat (population)
MBT - ^{13}C-Methacetin Breath Test
MCS - Molecular Correlation Spectrometry
MELD - Model for Endstage Liver Disease
mEA - modified Efficacy Analysis (set)
MMRM - Mixed Effect Repeated Measures (Model)
NAFLD - Nonalcoholic Fatty Liver Disease
NASH - Nonalcoholic Steatohepatitis
PDR - Percent Dose Recovery rate (expressed as % per hour)
PDR_{peak} - Maximal Percent Dose Recovery rate
PP - Per Protocol (analysis set)
PTFU - Post-Trial Follow-Up
QW - One per week
SA - Safety Analysis (set)

SAE - Serious Adverse Event
SAP - Statistical Analysis Plan
SBP - Spontaneous Bacterial Peritonitis
SD - Standard Deviation
SDV - Source Data Verification
SF - Screen Failures
SUSAR - Suspected unexpected serious adverse reaction
UADE - Unanticipated Adverse Device Effect
US - United States (of America)
USA - United States of America

2 INTRODUCTION

This Statistical Analysis Plan (SAP) was developed based on the original companion study protocol BMS-EX-0118 version 1.0, dated 20 February 2018, titled "Companion Protocol for the ^{13}C-Methacetin Breath Test (MBT) for use in Bristol-Myers Squibb phase 2b studies for BMS-986036 (PEG-FGF21), under Protocols MB130-068 and MB130-069". This SAP is an updated and more detailed companion to the "Statistical Methods" section of the original companion study protocol.

The original protocol and most of the study documents were written and maintained by Exalenz Bioscience Ltd. before being acquired by and integrated into Meridian Bioscience, Inc., and renamed Meridian Bioscience Israel Ltd. Therefore "Meridian" and "Exalenz" can be referred to as interchangeable terms in this SAP.

The companion protocol and this SAP describe how Exalenz intends to use the clinical data being obtained during the studies conducted by BMS sponsored IND studies: MB130-068 and MB130-069. The data collected as part of MB130-068 will be referred to as 'cohort 1' and the data collected as part of MB130-069 will be referred to as 'cohort 2'.

The enrollment phase and all MBT testing (incl. Day1, Week 24 and Week 48 visits) for the aforementioned BMS sponsored studies has been completed. The data is still being reviewed by BMS and the respective databases are planned to be made available to Exalenz between July and November 2021, after their respective data lock and release from BMS.

The initially planned sample size of 250 subjects, per statistical section in the companion protocol, was not reached for multiple reasons:

- The MBT testing as part of the BMS studies, was an opt in substudy, requiring an additional consent process. Subjects enrolled to the BMS studies were reluctant to add an additional investigational test to their study schedule.
- The COVID-19 outbreak further complicated the enrollment and especially the follow up testing of already enrolled subjects, as visits were more and more conducted remotely and any breath testing was avoided during in person visits.

Since the actual final sample size of subjects with valid MBT results at baseline and post-treatment phase, across both BMS studies, is expected to be lower than 80, the statistical analyses

for the study will be descriptive by nature. No formal statistical testing will be performed. Nominal p-values from statistical tests will be reported for suplementary information.

When differences exist in methods, descriptions or explanations provided in the protocol and this SAP, the SAP prevails.

Since this study is a companion to a pharmaceutical company's study, the data management for the main study can independently determine as to when a data freeze or a data lock shall be performed. Therefore, for the Exalenz companion protocol purposes, any amendments to the SAP will be made prior to Exalenz independently accessing the data from the database freeze or lock, if available. In case additional analyses not described in the final SAP or deviations from the final SAP are required, they will be documented in the Clinical Study Report (CSR).

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 *Study Objectives*

3.1.1 Primary Objective

The data generated in this companion study will be used to demonstrate the ability of the MBT to evaluate patient response to treatment with BMS-986036, comparing placebo to each treatment arm individually. Primary efficacy assessment will be performed using the Week 24 and the Week 48 visit measures compared to Day 1 (change from baseline) for the combined population of the two cohorts, according to availability, by dose of the BMS drug under study.

The same assessments for each study cohort independently will be reported.

3.1.2 Secondary Objective

The following assessments will be done by treatment arm by dose of the BMS drug under clinical invstigation and combined arms on the combined population of the two study cohorts:

1. To demonstrate the short and long-term prognostic value (3 months, 6 months and 1 year, respectively) of MBT for liver disease deterioration (reported as liver-related

clinical outcome events). Assessment will be performed using MBT from the Day 1, Week 24 and Week 48 visits.

2. To assess the ability of changes in the MBT to reflect biopsy proven changes in fibrosis and/or NAS as assessed by a central reader, where available, at Week 24 (or at least Week 20 in cases of an Early Termination time point) (for cohort 1) or at Week 48 (for cohort 2) compared to the baseline biopsy from the screening visit.

3. To assess the ability of changes in the MBT to reflect changes in liver stiffness as measured by Magnetic Resonance Elastography (MRE), where available, at Week 24 and Week 48 (or at Early Termination) compared to baseline MRE from the screening visit.

4. To assess the ability of changes in the MBT to reflect changes in Proton Density Fat Fraction (PDFF) as measured by Magnetic Resonance Imaging (MRI), where available, at Week 24 and Week 48 (or Early Termination), compared to baseline MRI from the screening visit.

5. To assess the ability of changes in the MBT to reflect changes in Serum Pro-C3, where available, at Week 24 and Week 48 of treatment (or Early Termination), compared to baseline Pro-C3 from the screening visit.

The same assessments for each study cohort independently will be reported.

The following additional objectives are applicable for cohort 2 only:

1. To assess the ability of changes in the MBT to reflect changes in liver stiffness as measured by “Fibroscan” elastography, where available, at the Week 48 visit (or earlier if there was an Early Termination) compared to the screening visit.

2. To assess the ability of changes in the MBT to reflect changes in the Model for End-stage Liver Disease (MELD) score, where available, at Week 24 and Week 48 visits compared to study Day 1.

3. To assess the ability of changes in the MBT to reflect changes in the Child-Turcotte-Pugh Scoring (CTP) score, where available, at Week 24 and Week 48 (or Early Termination) compared to study Day 1.

3.1.3 Exploratory Objective

- To assess the ability of the MBT to monitor patient status in comparison to other available measures, such as Liver Fibrosis stage, NAS, MELD, CTP, PDFF, Liver Stiffness, Serum Biomarker or Pro-C3.

3.1.4 Safety Objective

Evaluation of safety related to the MBT.

3.2 *Study Endpoints*

3.2.1 Primary Endpoint

The MBT's ability to measure the effect of BMS-986036 treatment on the metabolic capacity of the liver at Week 24 and Week 48 visits during the Double-Blind Treatment Period, as compared to changes in placebo treated subjects.

3.2.2 Secondary Endpoints

In order to assess the correlation of changes in MBT with changes in other measures of liver disease, the following endpoint measures will be collected, where available:

For all study cohorts: MBT results for each MBT visit (Day 1, Week 24, Week 48, or Early Termination visits) as well as changes in MBT results ($cPDR_{30}$, PDR_{peak} or other breath test parameters).

The other measures of liver disease that will also be collected in this study are as follows:

1. Liver-related Clinical Outcome defined as the first occurrence of any one of the following: all-cause mortality, MELD score ≥15, liver transplant, hepatocellular carcinoma (HCC), ascites requiring medical intervention, hospitalization (≥ 24 hours) for onset of variceal bleeding, hepatic encephalopathy and spontaneous bacterial peritonitis.
2. Liver Fibrosis stage and NAS as determined by Liver Biopsy assessed by a central reader.
3. Liver Stiffness as determined by MRE.
4. PDFF as determined by MRI.
5. Serum Biomarker Pro-C3.

Additional measures for cohort 2 include:

1. Liver Stiffness as determined by Fibroscan® Elastography
2. MELD scores
3. CTP scores

4 STUDY DESIGN

Please refer to BMS' protocols MB130-068 and MB130-069 - IND 125297.

This study is a feasibility companion protocol that will rely on the data generated by BMS's studies of BMS-986036 (PEG-FGF21) under protocols MB130-068 and MB130-069 (IND 125297), which are defined in this companion protocol as two separate study cohorts (1 and 2, respectively) with the exception of the MBT, for which Exalenz may extract additional data based on the recorded MBT results. The MB130-068 and MB130-069 studies are Phase 2b, multicenter, double-blind, randomized, placebo-controlled, parallel-group studies to demonstrate the safety and efficacy of BMS-986036 in the treatment of subjects with NASH and stage 3 liver fibrosis or compensated cirrhosis with up to 48 weeks of treatment. The study is feasibility for drug response monitoring however the data may be used by Exalenz for future submissions.

As described in the BMS protocols, subjects will be enrolled and randomized via interactive response technology (IRT) to receive BMS-9860936 10mg QW, BMS-986036 20mg QW, BMS-9860936 40mg QW or matching placebo QW in a 1:1:1:1 ratio.

The BMS studies' treatment durations will each consist of two periods:

1. A 48-week, Double-Blind Treatment Period, during which the subjects will receive blinded study medication (BMS-986036 10mg, 20 mg, 40mg QW or matching placebo QW). During the Double-Blind Treatment Period, subjects will be evaluated for safety and efficacy every 4 weeks (±5 days) through Week 24 and every 8 weeks (±5 days) from Week 24 through Week 48.
2. A Follow up period, during which subjects will be evaluated for safety and efficacy for 4 weeks through Week 52.

3. A Follow up period of at least 6 months and up to 14 months after the Week 52/ PTFU Visit for the collection of additional DXA assessment (in all participants) and immunogenicity assessments (in participants for whom Long-Term Immunogenicity Follow-Up Visits are required.) Any liver related complication event will be recorded.

The last dose of study medication will be at the Week 48 visit. Subjects will have a safety and efficacy evaluation at week 48 and return for a post-treatment follow-up evaluation through Week 52.

As a sub-study of BMS protocols MB130-068 and MB130-069, MBT will be performed at the Day 1 visit and every 24 weeks during the Double-Blind Treatment Period in order to allow the assessment whether BMS-986036 compared to placebo improves liver metabolic function as determined by the MBT.

4.1 *Sample Size Considerations*

Subjects, that were enrolled into two separate BMS sponsored IND studies (MB130-068, MB130-069, respectively) at selected study sites, were offered the opportunity to perform the MBT, and are considered as two separate study cohorts (cohort 1 and 2, respectively) for this companion protocol. Each cohort consists of four treatment arms (BMS-986036 10mg, 20mg, 40mg QW or matching placebo QW) as defined in the respective BMS sponsored protocols.

Cohort 1 consists of subjects with NASH and stage 3 fibrosis, as assessed by a central laboratory reader of the liver biopsies, and who meet all the MB130-068 study criteria. The sample size for this MB130-068 study is n=160.

Cohort 2 consists of subjects with NASH and compensated liver cirrhosis (stage 4 fibrosis) as assessed by a central laboratory reader of the liver biopsies, and who meet all the MB130-069 study criteria. The sample size for this MB130-069 study is n=100.

This feasibility companion protocol includes those two cohorts of subjects, which were planned for up to 260 subjects) from approximately 75 sites worldwide (USA and Japan) for the two BMS IND studies, while the MBT was only conducted in the USA.

It was expected that not all participating sites would elect to perform the MBT. The total number of subjects expected to perform the MBT was initlly planned for up to 250 subjects (also accounting for drop outs). Each subject would perform up to 3 MBTs over 1 year.

However, as aforementioned in the Introduction (section 2), the enrollment phase and all MBT testing (incl. Day1, Week 24 and Week 48 visits) for the aforementioned BMS sponsored studies has been completed. The data is still being assessed by BMS and the respective databases are planned to be made available to Exalenz between July and November 2021, after their respective data lock and release from BMS.

The initially planned sample size of 250 subjects, per statistical section in the companion protocol, was not reached for multiple reasons:

- The MBT testing as part of the BMS studies, was an opt in substudy, requiring an additional consent process. Subjects enrolled to the BMS studies were reluctant to add an additional investigational test to their study schedule.
- The COVID-19 outbreak further complicated the enrollment and especially the follow up testing of already enrolled subjects, as visits were more and more conducted remotely and any breath testing was avoided during in person visits.

Since the actual final sample size of subjects with valid MBT results at baseline and post-treatment phase, across both BMS studies, is expected to be lower than 80, the statistical analyses for the study will be descriptive by nature. No formal statistical testing will be performed. Nominal p-values from statistical tests will be reported for suplementary information.

5 GENERAL CONSIDERATIONS FOR HANDLING OF MISSING DATA

5.1 *Premature Withdrawal and Missing Data*

For patients who are withdrawn from the study prior to study completion, all data compiled up to the point of discontinuation will be used for analysis. All withdrawals will be included in all analyses up to the time of withdrawal.

There will be no imputation for missing data.

The study variables cannot be evaluated for subjects for whom BreathID® MCS device MBT results are not available and therefore these subjects will be left out of the efficacy analysis. Subjects missing clinical outcome or biopsy results or other endpoints will be excluded from the respective analyses.

6 SIGNIFICANCE LEVELS AND HANDLING OF TYPE I ERROR

6.1 *Type I Error*

All analyses in this study will be considered descriptive by nature. No formal statistical testing will be performed. Nominal p-values from statistical tests will be reported for suplementary information.

7 ANALYSIS SETS

7.1 *Safety Analysis Set (SA)*

The Safety Analysis set will include all subjects enrolled under BMS' MB130-068 and MB130-069 studies that initiated at least one MBT (had taken the ^{13}C-Methacetin solution), even if the MBT was not completed or the result was not valid.

7.2 *Efficacy Analysis Set (EA)*

The Efficacy Analysis set will include all subjects enrolled under BMS' MB130-068 and MB130-069 studies who have successfully performed the MBT test and did not have any major protocol deviations for the current study.

7.3 *Modified Efficacy Analysis Set (mEA)*

The modified Efficacy Analysis set will include all subjects enrolled under BMS' MB130-068 and MB130-069 studies who have successfully performed the MBT test. Visit specific major protocol deviation will be excluded, while keeping subjects in this analysis set for other valid visits.

Safety analyses will be performed on the SA set and efficacy analyses on the mEA set. Sensitivity analysis will be performed on the SA (corresponding to ITT) and EA set.

8 STATISTICAL ANALYSES

8.1 *General Considerations for Data Analyses*

All analyses will be performed using either SAS® v9.4 or higher (SAS Institute, Cary NC, US) or the R software version 4.0.3 or higher (R Development Core Team. Vienna, Austria).
The standard summary statistics for continuous variables are: N, mean, standard deviation, median, minimum and maximum. The standard summary statistics for categorical variables are: count and proportion.

The analyses will be descriptive by nature, nominal p-values will be reported for suplementary information. Any statistical tests performed, will be two-sided. The significance level of findings will be equal to or lower than 5%. Where confidence limits are appropriate, the confidence level will be 95%. Nominal p-values and unadjusted confidence intervals will be presented.

8.2 *Baseline Definitions*

The study baseline will be defined as the Day 1 visit value, unless specifically mentioned otherwise. In case of repeat measurements, the latest value associated with the Day 1 visit will be considered the baseline value.
For survival models: The baseline MBT test will be defined as the baseline and day 0 of follow up.

8.3 *Disposition of Patients*

Subject dispositions will be summarized based on all subjects screened into the study separated by study cohort (and combined), and for each treatment group.

The following subject disposition information will be presented:

- The number and percentage of subjects who had valid MBT for each visit.
- The number and percentage of reasons for not having a valid MBT for each visit.
- The number and percentages of subjects that were excluded from the EA and mEA analysis sets, by reason for exclusion.

8.4 *Efficacy Analyses*

8.4.1 Primary Endpoint

In order to show the ability of the MBT to measure the effect of BMS-986036 treatment on the metabolic capacity of the liver after Week 24 and Week 48 visits, as compared to changes in placebo treated subjects, the primary endpoint will be analyzed using a responder analysis, where any increase of MBT value will be considered as a response while a same value or a decrease of the MBT value will be considered as non-respose.

The primary analysis will be conducted on the mEA set, with the PDR_{peak} and $cPDR_{30}$ responder rate of Week 24 and Week 48 of data from both BMS' studies.

Individual analyses for each cohort separately will also be reported.

8.4.2 Secondary Endpoints

8.4.2.1 Prognostic Value of MBT in Overall Event-Free Survival

In order to assess the prognostic value of MBT in prediction of liver disease deterioration (reported as liver-related clinical outcome events), the endpoint measures will be point estimates of Cox Regression's Hazard Ratio for classifying Subjects into risk groups for clinical deterioration with respective exact two-sided 95% confidence intervals in the placebo and treatment arms as determined by MBT. The MBT parameter to be used to predict liver-related clinical outcome events is PDR_{peak}. Any PDR_{peak} value of less or equal to 20 %/h (see **Appendix A** for detailed description of parameter calculation) will be considered as 'high risk' and any value above that threshold will be considered as 'lesser risk' (additional cut-off values may be explored). The dichotomic MBT result will be tested for significance using the Cox proportional hazards regression model with site and randomized arm as covariates. If the randomized arm factor is found non-significant (i.e. p-value > 0.05), then this factor will not be a covariate for the main analysis to be performed. If the randomized arm factor is found statistically significant (i.e. p-value ≤ 0.05), then the main analysis will be performed keeping this factor as a covariate (to 'adjust' the analysis for treatment).

The time-to-first event will be derived as the number of days between the Day 1 MBT test and the date when the first event occurs or when a subject is censored (i.e., event/censored date minus

Day 1 MBT date plus 1). Subjects will be censored at their last study visit for the following reasons:

- If a subject discontinues the study prior to the end of the study without experiencing an event
- If a subject reaches the Final Treatment visit without experiencing an event

Survival analysis will be conducted using the Cox proportional hazard model. The model summary will include the number of subjects in the model, and a table with each covariate in a separate line specifying the coefficient's value, Hazard Ratio, Hazard Ratio 95% Confidence Interval and p-value. In addition, a Kaplan-Meier plot for event-free survival will be presented, stratified by MBT parameter along with the MBT parameter log-rank p-value. Additionally, a crosstab table of MBT parameter and events will be presented.

8.4.2.2 Correlations between changes in MBT parameters and changes in other liver related parameters

Repeat MBT results ($cPDR_{30}$,PDR_{peak} or other breath test parameters) and their changes in subjects with and without treatment (BMS-986036) for nonalcoholic steatohepatitis (NASH) at Day 1, Week 24 and Week 48 (or Early Termination visits) will be compared and tested for correlation to baseline, as well as repeat results (change from baseline), for the following measurements:

a. Biopsy based Fibrosis and/or NAS score
b. Liver stiffness as measured by MRE
c. PDFF as measured by MRI
d. Serum Pro-C3 results
e. Liver elastography by Fibroscan (in cohort 2 only)
f. MELD scores (in cohort 2 only)
g. CTP scores (in cohort 2 only)

Linear Regression will be applied in order to test for significance of the correlations between MBT and the liver measurements listed above.

Changes in MBT are measured as the difference between baseline and each of the MBT visits as well as the change in measurements between two subsequent visits in each of the two treatment groups.

The metabolic capacity of the liver as determined by the MBT PDR_{peak} and $cPDR_{30}$ will be the main MBT parameters of interest.

Nevertheless, available breath test parameters (Delta Over Baseline - DOB at the respective times) will be collected from the completed eCRFs. The DOBs will be transformed to percentage dose recovery – PDR, by normalizing the DOB using patient weight and height. The Area under the DOB and under the PDR curve will be calculated at 5-minute time intervals resulting in cDOB and cPDR at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 and 60 minutes respectively. Analyses may be done using any of the MBT derived parameters.

8.5 *Site Poolability*

Primary efficacy analysis will be reported for each cohort separately as well as for each site/ group of sites (see next section) separately.

For sites with less than 10 subjects, the following pooling of sites method will be applied for each cohort separately: Sites will be sorted from smallest to largest based on the number of randomized subjects with valid baseline MBT results. The smallest site will be pooled with the second smallest, and if necessary with the next sites in line until the site group reaches 10 subjects or more. The site value for those sites will be assigned "Site Group 1". Then the next site in line, if lower than 10 subjects, will be pooled with the sites after it until the site group reaches at least 10, and so forth until all sites or site groups have at least 10 subjects. Furthermore, site by MBT dichotomy interaction will be added to the Linear and Cox regression models as a covariate to test for site effect on the exploratory endpoints.

8.6 *Safety Analyses*

The adverse events possibly or probably related to Methacetin and/or the BreathID® MCS device will be presented along with a two sided 95% exact binomial confidence interval. The analysis of all adverse events will include incidence tables and will include analyses by severity, relationship to device or drug and baseline variables.

No inferential statistical testing will be performed for safety variables.

APPENDIX A - – METHACETIN BREATH TEST PARAMETERS

The BreathID MCS System measures the change of the $^{13}CO_2/^{12}CO_2$ ratio in exhaled breath following ingestion of ^{13}C-Methacetin compared to the $^{13}CO_2/^{12}CO_2$ ratio before ingestion. This measure is called 'Delta Over Baseline' (DOB) and is automatically measured every 2-3 minutes, resulting in approximately 23 DOB's and corresponding time points over one hour. Subjects visit height and weight as well as all available DOB measures with corresponding time point (T) will be retrieved from the completed eCRFs.

1. DOB values must be sorted by time before any calculation, while a first pair of data points should always be added with time T_0=0 min and DOB_0 =0.

2. The DOBs will be transformed into percentage dose recovery rates (PDRs) by normalizing the DOB using patient body weight and height at each observed time point (i) by using the following formula:

$$PDR_i = 0.01817853 \cdot DOB_i \cdot Weight^{0.5378} \cdot Height^{0.3963}$$

While Weight is in kg, and Height is in cm
The units of PDR is %/hour

3. The maximum rate at which metabolism occurs results in a peak value of the breath test called DOB_{Peak} and PDR_{Peak}, respectively. Both occur at the same time, which is called the Peak time.
   a. **DOB_{peak}**: DOB_{peak} is defined as the maximum DOB.

$$DOB_{peak} = \max(DOB_0, DOB_1, DOB_2, \ldots, DOB_{24})$$

   b. **PDR_{peak}**: PDR_{peak} is defined as the maximum PDR.

$$PDR_{peak} = \max(PDR_0, PDR_1, PDR_2, \ldots, PDR_{24})$$

4. The area under the DOB curve will be calculated for each time point. This area represents the cumulative DOB (cDOB) at any given time point.
   a. **DOB_{x_min} and $cDOB_{x\_min}$**: The following steps will be followed to obtain the DOB and cDOB at 5 minutes intervals (e.g. 5, 10, 15,…,60 min), where 'x' is 05, 10, 15, …, 60 respectively. For each 'x' the following steps shall be followed:

b. Find 'a', the index for which:

$$T_{a-1} < x \leq T_a$$

c. Calculate **DOB_{x_min}** using the following formula:

$$DOB_{x\_min} = DOB_{a-1} + \frac{DOB_a - DOB_{a-1}}{T_a - T_{a-1}} \cdot (x - T_{a-1})$$

d. Calculate **$cDOB_{x\_min}$** using the following formula:

$$cDOB_{x\_min} = \sum_{i=1}^{a-1} \left(\frac{\frac{T_i - T_{i-1}}{60} \cdot (DOB_i + DOB_{i-1})}{2} \right) + \frac{\frac{x - T_{a-1}}{60} \cdot (DOB_{x\_min} + DOB_{a-1})}{2}$$

MBT parameters results that do not have data points for at least 'x' minutes cannot be calculated

5. The PDR as well as the area under the PDR curve will be calculated for each time point. This area represents the cumulative PDR (cPDR) at any given time point in units of %.

a. **PDR_{x_min} and $cPDR_{x\_min}$**: The following steps will be followed to obtain the PDR and cPDR at 5 minutes intervals (e.g. 5, 10, 15,…,60 min), where 'x' is 05, 10, 15, …, 60 respectively. For each 'x' the following steps shall be followed:

b. Find 'a', the index for which:

$$T_{a-1} < x \leq T_a$$

c. Calculate **PDR_{x_min}** using the following formula:

$$PDR_{x\_min} = PDR_{a-1} + \frac{PDR_a - PDR_{a-1}}{T_a - T_{a-1}} \cdot (x - T_{a-1})$$

d. Calculate **$cPDR_{x\_min}$** using the following formula:

$$cPDR_{x\_min} = \sum_{i=1}^{a-1} \left(\frac{\frac{T_i - T_{i-1}}{60} \cdot (PDR_i + PDR_{i-1})}{2} \right) + \frac{\frac{x - T_{a-1}}{60} \cdot (PDR_{x\_min} + PDR_{a-1})}{2}$$

MBT parameters results that do not have data points for at least 'n' minutes cannot be calculated

6. The cDOB and cPDR at the peak time are called $cDOB_{peak}$ and $cPDR_{peak}$, respectively. They are calculated as described in steps 4 and 5, respectively, while 'x' is the actual time 'T' of the observed peak value. The $cPDR_{peak}$ divided by Peak time is named cPDRpeak_div_Peaktime.

7. The following list of MBT result parameters will thus be used in the statistical analysis: DOB_{peak}, $cDOB_{peak}$, PDR_{peak}, $cPDR_{peak}$, cPDRpeak_div_Peaktime, Time to Peak, DOB_{5_min}, DOB_{10_min}, DOB_{15_min}, DOB_{20_min}, DOB_{25_min}, DOB_{30_min}, DOB_{35_min}, DOB_{40_min}, DOB_{45_min}, DOB_{50_min}, DOB_{55_min}, DOB_{60_min}, $cDOB_{5\_min}$, $cDOB_{10\_min}$, $cDOB_{15\_min}$, $cDOB_{20\_min}$, $cDOB_{25\_min}$, $cDOB_{30\_min}$, $cDOB_{35\_min}$, $cDOB_{40\_min}$, $cDOB_{45\_min}$, $cDOB_{50\_min}$, $cDOB_{55\_min}$, $cDOB_{60\_min}$, PDR_{5_min}, PDR_{10_min}, PDR_{15_min}, PDR_{20_min}, PDR_{25_min}, PDR_{30_min}, PDR_{35_min}, PDR_{40_min}, PDR_{45_min}, PDR_{50_min}, PDR_{55_min}, PDR_{60_min}, $cPDR_{5\_min}$, $cPDR_{10\_min}$, $cPDR_{15\_min}$, $cPDR_{20\_min}$, $cPDR_{25\_min}$, $cPDR_{30\_min}$, $cPDR_{35\_min}$, $cPDR_{40\_min}$, $cPDR_{45\_min}$, $cPDR_{50\_min}$, $cPDR_{55\_min}$, $cPDR_{60\_min}$.