NOVARTIS

Clinical Development

VAL489/Valsartan

Clinical Trial Protocol CVAL489K2306

A 6 week, randomized, multicenter, double-blind, double-dummy study to evaluate the dose response of valsartan on blood pressure reduction in children 1-5 years old with hypertension, with or without chronic kidney disease, followed by a 20 week open-label titration phase

RAP Module 3 – Detailed Statistical Methodology

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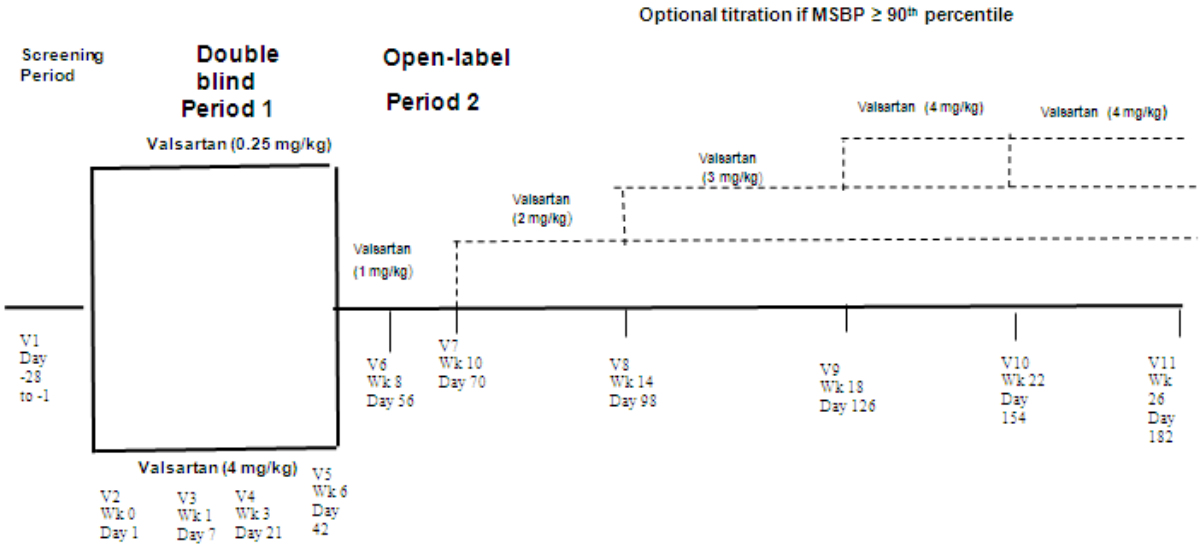
9.7 Statistical methods planned in the protocol and determination of sample size

Data will be analyzed by according to the data analysis section 9 of the study protocol that is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

An overview of the study design is presented in the following figure:



9.7.1 Statistical and analytical plans

9.7.1.1 Subjects and treatments

The following analysis populations will be defined for statistical analyses:

Randomized Set (RAN) - All patients who receive a randomization number, regardless of receiving double blind study medication.

Full-analysis Set (FAS) - All patients randomized with at least one follow-up efficacy assessment in the double blind phase. Following the intent-to-treat principle, patients will be analyzed according to the treatment assigned at randomization. However, patients who were not qualified for randomization and were inadvertently randomized into the study are excluded from the FAS, provided these patients did not receive study drug.

Per-protocol Set (PPS) - All patients in FAS without any major protocol deviations in the double-blind phase. The major protocol deviations will be pre-specified prior to unblinding the treatment codes for analyses.

Safety Set (SAF) - All patients who received at least one dose of study medication in the double blind phase. Patients will be analyzed according to treatment they received.

Open-label Full Analysis Set (OFAS) - All patients entering the open label phase with at least one follow-up efficacy assessment during open label phase.

Open-label Safety Set (OSAF) - All patients who received at least one dose of study medication in open-label phase.

Subject disposition will be summarized for the following three periods: screening period (for all screened patients), double-blind period (period 1) and open-label period (period 2). The number of patients for the analysis sets will be provided.

Table 1 Subject Classification

Analysis Set	PD severity codes that cause subjects to be excluded	Non-PD criteria that cause a subject to be excluded
RAN	NA	Not randomized
FAS	8	Not in RAN; Mistakenly randomized and not receive study drug; No post-randomization assessment of any efficacy variables during the double-blind treatment period
PPS	1*, 8	Not in FAS;
SAF	5, 8	NA
OFAS	8	No post-randomization assessment of any efficacy variables during the open label treatment period
OSAF	5,8	Not received any study medication in open-label phase

* PDs with which occurred in the open-label phase do not lead to exclusion from FAS, PPS or SAF.

The severity codes of PDs causing subjects to be excluded from analysis set are recorded in the latest version of VAP M3 document. Protocol deviations (with and without leading to exclusion from analysis sets) will be summarized during the double-blind period for RAN and also during the open-label period 2 for the randomized patients who entered the open-label period 2.

For RAN, summary statistics will be provided by treatment group for demographics and other baseline characteristics including age, height, weight, BMI, head circumference, MSBP (mean systolic blood pressure), MDBP (mean diastolic blood pressure), pulse, as continuous variables and gender, race, ethnicity, continuing use of prior antihypertensive treatment

(Yes/No), CKD (chronic kidney disease) /non-CKD as qualitative variables. Comparisons of treatment groups with respect to the demographics and baseline characteristics will be performed using chi-square tests or a t test as appropriate. The results of these tests are provided for descriptive purposes, and will not be used as a formal basis to determine the factors to be included in statistical models.

Relevant medical history and current medical conditions will be summarized by treatment group for RAN.

Study drug exposure in Period 1 (double-blind phase):

Duration (in days) of exposure to study drug in Period 1 will be computed and summarized by treatment group(for all patients as well) for SAF as follows.

last study drug date in Period 1 – study drug start date in Period 1+ 1,

or

last visit date in Period 1 – study drug start date in Period 1 if the last study drug date in Period 1 is missing or incomplete.

Study drug start date in Period 1 is Visit 2 date. Last study drug date in Period 1 is the last known study drug date from the study phase completion panel.

Study drug exposure in Period 2 (open-label phase):

Duration (in days) of exposure to study drug in period 2 will be summarized by each dose, i.e. 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg (and non-protocol defined dose, if any) as well as total exposure on any dose for OSAF as follows.

The total study drug exposure to any dose in Period 2 is calculated as below:

Last study drug date in Period 2 – study drug start date in Period 2 +1

or

last visit date in Period 2 – study drug start date in Period 2 if the last study drug date in Period 2 is missing or incomplete.

Study drug start date in Period 2 is Visit 5 date. Last study drug date in Period 2 is the last known study drug date from the study completion panel.

Start and end dates for individual doses will be used to calculate duration of exposure by dose. For each dose, duration of total exposure to each specific dose will be derived accordingly.

In addition, duration (in days) of exposure to study drug during the entire study (with Period 1 and Period 2 together) will be summarized similarly by dose and overall (including all doses) for SAF.

Prior and concomitant antihypertensive medications taken during the study will be summarized by treatment for the following 3 periods separately: prior to taking study medication by double-blind treatment in SAF, double-blind treatment period 1 by treatment in SAF and open-level period 2 in OSAF. Concomitant non-antihypertensive medications and significant non-drug therapies during the study will be summarized for (i) prior to study drug and (ii) after study drug.

The same summaries as above will be performed for the subgroups of CKD and non-CKD patients.

9.7.1.2 Efficacy evaluation

9.7.1.2.1 Analysis of the primary variable(s)

The primary objective is to evaluate if a dose dependent reduction in MSBP exists when comparing two doses of valsartan solution (0.25 mg/kg and 4 mg/kg) over a 6 week period in children 1-5 years old with hypertension (MSBP $\geq 95^{th}$ percentile for age, gender and height), with or without CKD.

The primary efficacy variable is change from baseline (Visit 2) in mean systolic blood pressure (MSBP) at Week 6 endpoint during the double-blind period 1. The primary analysis will be performed on the FAS.

Statistical hypothesis, model, and method of analysis

The null hypothesis is that there is no treatment difference in the reduction of MSBP (mmHg) between dose groups 0.25mg/kg (low) and 4 mg/kg (high). The alternative hypothesis is that there is a difference between dose groups 0.25 mg/kg and 4 mg/kg. The hypotheses were expressed as follows:

$H_0: \delta_{low} = \delta_{high}$ *versus* $H_1: \delta_{low} \neq \delta_{high}$

where δs are the mean changes from baseline at Week 6 endpoint in MSBP in the treatment group indicated.

The treatment comparison will be tested at a two-sided significance level of 0.05. The change from baseline in MSBP at Week 6 endpoint during double-blind phase will be analyzed in the FAS using an analysis of covariance model (ANCOVA) as the primary analysis model with treatment and CKD strata as factors and baseline MSBP as the covariate. The baseline MSBP values will be centered by subtracting the overall mean of all patients included in the analysis for FAS. For patients with missing values at Week 6, the last post-baseline observation during the double-blind period will be carried forward (LOCF) as the Week 6 endpoint. CKD strata (yes/no) are the stratification factor used for IRT randomization. When the investigator entered a wrong stratification stratum in IRT, a protocol deviation (PD code = S01) is registered and the correct stratification factor is used for all analyses. The estimated treatment difference for the treatment comparison will be tabulated along with the associated 95% confidence interval and two-sided p-value. Treatment by baseline MSBP interaction will be examined by adding the treatment-by-baseline-MSBP term to the primary analysis model. The results of this assessment will be presented in the CSR section 16.1.9.

Supportive analyses

In addition to the primary analysis based on the FAS population, a similar analysis for the primary endpoint will also be performed on the PPS population as a supplementary assessment.

To further assess the dose response, the change from baseline at Week 6 endpoint in MSBP will be analyzed in FAS by an analysis of covariance model with CKD strata as the factor and baseline MSBP as a covariate, and dose per body weight (mg/kg) as the main regressor. The estimated slope with 95% confidence interval and p-value for the dose per body weight will be provided.

Subgroup analysis for CKD/non CKD patients

Similar analysis of the primary efficacy variable for the treatment comparison will be performed for the subgroup of CKD patients and for the subgroup of non-CKD patients (per CKD yes/no strata). The estimated treatment difference, 95% confidence interval and two-sided p-value for the treatment comparison within each subgroup analysis will be provided. Furthermore, treatment-by-CKD strata interaction in the entire FAS will be assessed by inclusion of the additional interaction term to the primary analysis model for the overall analysis in FAS and the p-value for the respective interaction term will be provided.

Descriptive statistics

The change from baseline in MSBP (together with the corresponding baseline and post-baseline MSBP) during double-blind phase will be summarized by treatment and visit (including Week 6 LOCF endpoint) for the FAS (for overall as well as for each of the CKD/non-CKD subgroup) . The MSBP will be plotted versus visit (not including Week 6 LOCF endpoint) by treatment group for the FAS (for overall as well as for each of CKD/non-CKD subgroup). In addition, change from baseline in MSBP will also be plotted versus visit by treatment group for the FAS (for overall as well as for each of CKD/non-CKD subgroup).

9.7.1.2.2 Analysis of secondary variable(s)

The two-sided 0.05 significance level and 95% confidence interval will be provided for the following analyses as applicable. The analyses described below will be carried out in FAS for the double-blind period 1 and in OFAS for the open-label period 2.

Period 1

Change from baseline in mean diastolic blood pressure (MDBP)

Similar analysis as for MSBP will be performed for MDBP to evaluate the reduction of MDBP from baseline. Change from baseline at Week 6 endpoint in the double-blind period (using LOCF) in MDBP will be analyzed for FAS patients using an analysis of covariance (ANCOVA) model with treatment and CKD strata as factors and baseline MDBP as the covariate. Treatment comparison will be performed at the two-sided significance level of 0.05. The estimated treatment effects, treatment difference, 95% confidence interval, and p-value for the treatment comparison will be provided. In addition, similar supportive analysis for PPS will be also provided.

Similar summary statistics and plots as for MSBP will be provided for change from baseline in MDBP.

Percentage of patients achieving MSBP < 90th percentile for age, gender and height

Percentage of patients achieving MSBP < 90^{th} percentile for age, gender and height at Week 6 endpoint will be analyzed using a logistic regression model with treatment and CKD strata as

factors and baseline MSBP as the covariate. The odds ratio of Valsartan 4.0 mg/kg / Valsartan 0.25 mg/kg will be computed, along with the associated 95% confidence interval and p-value. In addition, the number and % of patients achieving MSBP < 90th percentile for age, gender and height will be summarized by treatment and visit (including the Week 6 endpoint). Similar analyses will be carried out for the CKD and non-CKD subgroups of patients.

Percentage of patients achieving MSBP < 95th percentile for age, gender and height

Percentage of patients achieving MSBP < 95th percentile for age, gender and height at Week 6 endpoint will be also analyzed using a logistic regression model with treatment and CKD strata as factors and baseline MSBP as the covariate. The odds ratio of Valsartan 4.0 mg/kg / Valsartan 0.25 mg/kg will be computed, along with the associated 95% confidence interval and p-value. In addition, the number (and %) of patients achieving MSBP < 95th percentile for age, gender and height will be summarized by treatment and visit (including the Week 6 endpoint). Similar analyses will be carried out for the CKD and non-CKD subgroups of patients.

Percentage of patients achieving both MSBP and MDBP < 90th percentile for age, gender and height; percentage of patients achieving both MSBP and MDBP < 95th percentile for age, gender and heights.

Percentage of patients achieving both MSBP and MDBP < 90th percentile for age, gender and height at Week 6 endpoint will be analyzed using a logistic regression model with treatment and CKD strata as factors and baseline MSBP as the covariate. The odds ratio of Valsartan 4.0 mg/kg / Valsartan 0.25 mg/kg will be computed, along with the associated 95% confidence interval and p-value. In addition, the number (and %) of patients achieving both MSBP and MDBP < 90th percentile for age, gender and height will be summarized by treatment and visit (including the Week 6 endpoint). Similar analyses will be carried out for the CKD and non-CKD subgroups of patients.

Similar analyses will be also performed for the percentage of patients achieving both MSBP and MDBP < 95th percentile for age, gender and height at Week 6 endpoint.

UACR (Urine Albumin Creatinine Ratio) in CKD patients

UACR was collected for CKD patients only. The UACR value at a given visit for a patient is to be derived by the median of the three lab values collected for that visit. The UACR value will be assessed in the CKD patients.

Change from baseline in log(base 10)-transformed UACR will be analyzed using an ANCOVA model with treatment as a factor and log (base 10)-transformed baseline UACR as a covariate. The estimated treatment effects, treatment difference, 95% confidence interval, and p-value for the treatment comparison will be provided. The estimates to be presented will be in back-transformed scale.

Instead of the specified % change from baseline in UACR <= 25% in the protocol, the UACR response is to be defined as a percentage reduction from baseline in UACR ⩾ 25%. The proportion of patients with UACR response at Week 6 endpoint (LOCF) will be analyzed using a logistic regression with treatment as a factor and baseline UACR as a covariate. The odds ratio of Valsartan 4.0 mg/kg / Valsartan 0.25 mg/kg will be computed, along with the associated 95% confidence interval and p-value.

Summary statistics (n, mean, standard deviation, median, min, max, geometric mean) of the UACR values for baseline, Week 6 endpoint and the respective change (from baseline at Week 6 endpoint) will be provided by treatment group. The number and percent of patients will be summarized by treatment group for each of the following categories in change from baseline at Week 6 endpoint: >= 25% reduction, change is less than 25% in positive/negative direction, and >=25% increase. Similar summary will be also provided by treatment group for the following categories: : >= 50% reduction, change is less than 50% in positive/negative direction and >=50% increase.

Cystain C GFR (Glomerular filtration rate) in CKD patients

cGFR (Cystain C GFR) was collected and assessed for CKD patients only.

Change from baseline in log(base 10)-transformed cGFR will be analyzed using an ANCOVA model with treatment as a factor and log(base 10)-transformed baseline cGFR as a covariate. The estimated treatment effects, treatment difference, 95% confidence interval and p-value for the treatment comparison will be provided. The estimates to be presented will be in back-transformed scale.

Summary statistics (n, mean, standard deviation, median, min, max, geometric mean) of the cGFR values for baseline, Week 6 endpoint and the respective change (from baseline at Week 6 endpoint) will be provided by treatment group.

Period 2

The efficacy data during the open-label period 2 will be assessed based on the summary statistics and plots below in OFAS. The summaries and plots will be presented with one single arm including all patients evaluated in the open-label period 2.

1. Change from baseline (Visit 2) in MSBP (together with the corresponding baseline and post-baseline MSBP) will be summarized (with n, mean, standard deviation, median, min, and max) by visit (including LOCF endpoint at end of the open-label period 2) during the open-label period 2. Similar summary will be provided for MDBP. Similar summaries for MSBP and MDBP will also be provided for the CKD and non-CKD subgroups. In addition, similar plots as for MSBP/MDBP in the double-blind period will be provided with one single arm for the OFAS in the open-label period 2.
2. Percentage of patients achieving MSBP < 90^{th} percentile (as well as MSBP < 95^{th} percentile, both MSBP/MDBP < 90^{th} percentile, and both MSBP/MDBP < 95^{th} percentile) for age, gender and height will be summarized by visit during the open-

label period 2. In addition, similar summaries will be provided for the CKD and non-CKD patients

3. In the CKD patients, change from baseline in UACR (together with the corresponding baseline and post-baseline UACR) will be summarized (with n, mean, standard deviation, median, min, max and geometric mean) by visit during the open-label period 2. In addition, the n and percentage of CKD patients in the categories of UACR changes (as defined in the assessment during the period 1) will be provided by visit during the open-label period 2.
4. In the CKD patients, change from baseline in cGFR (together with the corresponding baseline and post-baseline cGFR) will be summarized (with n, mean, standard deviation, median, min, max and geometric mean) by visit during the open-label period 2.

9.7.1.3 Safety evaluation

The safety (SAF) and open-label safety (OSAF) populations will be used as appropriate for summaries of the double-blind and open-label phases, respectively. Unless specified otherwise, comparison will be made to Baseline, which will be the measurement taken at Day 1 (Visit 2), or the sample obtained at an earlier visit (scheduled or unscheduled) which is closest to Day 1 if Day 1 measurement is missing.

9.7.1.3.1 Adverse Events

The number and percentage of patients reporting any adverse event during the double-blind treatment period and open-label phase will be summarized by primary system organ class, preferred term, and treatment (only for double-blind phase). Adverse events that are suspected to be related to study drug will be summarized. The maximum severity of all adverse events will be summarized. Serious adverse events and adverse events leading to study drug discontinuation (based on CRF AE data) will be summarized by primary system organ class, preferred term, and treatment (only for double-blind phase), and will be listed by patient.

In addition, all summaries will also be performed for the subgroups of CKD and non-CKD patients for double-blind phase and open-label phase, respectively.

9.7.1.3.2 Laboratory values

The details of lab parameters collected, SI units (note, only SI units will be reported), and normal ranges will be listed in CSR Section 16.

Table 2 Laboratory schedules by study protocol

Safety measurement	Visit
Standard hematology: Red blood cell count, hemoglobin, hematocrit, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count	Visits 1, 2, 5, 8, 9, 10 and 11

Safety measurement	**Visit**
Complete blood chemistry : Creatinine, non-fasting glucose, total bilirubin, AST/SGOT, ALT/SGPT, ALP, sodium, potassium, bicarbonate (total CO_2), chloride, calcium, phosphorous, total protein, albumin, uric acid, cholesterol, triglycerides and eGFR	Visits 1, 2, 5, 8 and 11
Abbreviated blood chemistry: Urea, creatinine, sodium, potassium, bicarbonate (total CO_2) and eGFR	Visits 9, and 10
Cystatin C GFR for CKD patients	Visits 2, 5, 10 and 11
Standard urinalysis: pH, specific gravity, glucose, protein, bilirubin, ketones, leukocytes, blood	Visits 1, 2, 5, and 11
Urinary albumin creatinine ratio (UACR) for CKD patients	Visits 2, 5, 10, and 11

Laboratory data will be summarized at baseline, endpoint of Period 1 (using LOCF) and endpoint of Period 2 (using LOCF) for absolute values and changes from baseline for each treatment. Baseline is defined as the last non-missing value prior to or at Week 0 (Visit 2). Laboratory shift tables are presented using normal ranges. In addition, the number and percentage of patients meeting pre-specified notable percentage change (see below) from baseline to any post-baseline result will be summarized. Separate listings are provided for hematology, blood chemistry, and urinalysis.

Pre-specified notable percentage changes for laboratory tests

Hematology

Erythrocyte count	>50% increase, >30% decrease
Hemoglobin	>50% increase, >30% decrease
Hematocrit	>50% increase, >30% decrease
Leukocyte count	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease

Blood Chemistry

Albumin	>50% increase, >25% decrease
BUN	>50% increase
Creatinine	>50% increase
Glucose	>50% increase, >50% decrease

Total bilirubin	>100% increase
SGOT / AST	>150% increase
SGPT / ALT	>150% increase
Sodium	>5% decrease
Potassium	>20% increase, >20% decrease
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease
Uric Acid	>50% increase
GFR (Schwartz)	>25% decrease

*Protocol stated that the laboratory variable is “urea”. BUN (blood urea nitrogen) was reported in the study. Both urea and BUN were analyzed using the same analytical test and were identical when expressed in mmol/L.

Programming notes: the attached spreadsheet provides details regarding the parameters included in each laboratory relevant output.

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In addition, the number and percentage of patients meeting pre-specified selected notable absolute biochemistry values (see below) will be summarized.(Table 3) will be summarized.

Table 3 Pre-specified selected notable absolute values for laboratory tests

Laboratory Variables	**Notable criteria**
Total bilirubin	> 2 x upper limit of the reference range
SGOT	> 3 x upper limit of the reference range > 5 x upper limit of the reference range > 8 x upper limit of the reference range > 10 x upper limit of the reference range
SGPT	> 3 x upper limit of the reference range > 5 x upper limit of the reference range > 8 x upper limit of the reference range > 10 x upper limit of the reference range
Potassium	> 5.3 mEq/L > 5.5 mEq/L

	> 6.0 mEq/L

9.7.1.3.3 Vital signs and other safety assessments

The change from baseline in pulse, height, body weight, and head circumference will be summarized by treatment (only for double-blind phase) and visit for both periods.

The number of subjects with or without clinically significant ECG abnormalities at each ECG assessment will be tabulated.

The taste assessment will also be summarized on SAF.

9.7.1.4 Interim analyses

NA

9.7.1.5 Other topics

NA

9.7.2 Determination of sample size

The sample size of 116 completed patients is calculated based on the primary efficacy variable, change from baseline in mean systolic blood pressure, and a standard deviation of 11 mmHg (based on previous data) is used. The sample size is calculated to ensure at least 80% power to detect statistical significance for the comparison valsartan 0.25 mg/kg versus valsartan 4 mg/kg under the alternative hypothesis that the treatment difference is 6 mmHg at a two-sided significance level of 0.05. Assuming 10% drop-out rate, the total targeted sample size to be randomized is 130 patients.

10 Clinical Study Report - Appendix 16.1.9 Documentation of statistical methods

10.1 Introduction

This appendix gives details about statistical methods in addition to the report text. All analyses will be performed using SAS Version 9.4 in a UNIX environment.

10.2 Definition of pooled centers for efficacy analysis

Due to small sample size at most individual study centers, data from centers within a geographic region will be pooled for the efficacy analysis. Center pooling will be pre-defined prior to the database lock and used in the efficacy analyses. If one or two particular centers

have substantially larger enrollment than other centers in one geographic area, the "super center" may be left as one group by itself.

10.3 Sample SAS program for efficacy analyses

The SAS code provided is intended to reflect the type of analyses planned; however, the actual code used may not be a verbatim of this example. The variable names used in this code were selected for understanding of the methodology and do not necessarily reflect the actual variable names in the data.

ANCOVA model for primary analysis

For the ANCOVA model in the analysis of change from baseline in MSBP at Week 6, the following SAS code are used:

```
PROC MIXED DATA=eff;
CLASS treatment CKD;
WHERE population = population (FAS);
MODEL response= treatment  CKD  baseline_MSBP;
ESTIMATE 'Valsartan High dose vs. Valsartan Low dose' treatment 1 -1/CL;
run;
```

- "eff" denotes the efficacy data set containing individual observations for the change from baseline in MSBP
- "treatment" denotes the variable containing the treatment groups (Low, High)
- "CKD" denotes the variable containing the CKD strata (CKD and non-CKD)
- "baseline_MSBP" denotes the centered baseline variable containing individual patient baseline MSBP deviation from the mean of all FAS patients.

Logistic regression model

The SAS procedure MIXED is used with the following SAS code:

```
proc logistic data=eff;
  class treatment CKD/(param=ref ref='Low');
  model response = trt base;
  contrast 'High dose vs. Low dose' treatment 1  -1 / estimate=exp;
run;
```

where `y`, `region`, `trt`, and `base` denote control or response variable, region, treatment, and baseline value (msSBP, or msDBP for y involving only msDBP) respectively.

The odds ratio of High dose /Low dose will be computed, along with associated 95% confidence intervals.

Comparability of baseline characteristics

Baseline comparability between the three treatment groups, for continuous parameters, was tested using two-sample t-test:

```
proc ttest;
  class treatment;
  variable <Quantitative baseline variable>;
run;
```

Baseline comparability between treatment groups, for categorical parameters, was tested using a CMH chi square-test:

```
proc freq ;
  tables treatment* < Qualitative baseline variable > / cmh noprint;
  output out=<output dataset> cmhga;
run;
```