A Phase 2 Open-label Extension Study to Assess the Safety of Continued Administration of MDV3100 in Subjects with Prostate Cancer Who Showed Benefit from Prior Exposure to MDV3100

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STATISTICAL ANALYSIS PLAN

Final version 1.0, dated 08-April-2015

A Phase 2 open-label extension study to assess the safety of continued administration of MDV3100 in subjects with Prostate Cancer who showed benefit from prior exposure to MDV3100

Protocol Version 4.0, 03-July-2014

Phase 2 Study of MDV3100

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
BMI	Body Mass Index
CA	Competent Authority
CRF	Case Report Form
CT	Computed Tomography
CV	Coefficient of Variation
CXR	Chest X Ray
CYP	Cytochrome P450
DRM	Data Review Meeting
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
e.g.	Exempli Gratia (for example)
ESV	End of Study Visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
ICF	Informed Consent Form
ISN	International Study Number
LLOQ	Lower Limit of Quantification
MDV3100	Study Drug
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MRI	Magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
PK	Pharmacokinetic
PSA	Prostate-specific Antigen
PT	Preferred Term
s	Second
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
WHO-DRL	World Health Organization Drug Reference list

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. The SAP is finalized and signed prior to hard lock of the database.

2 VISIT SCHEDULE

Table 1 Schedule of Assessments

Study Day	**-32 to -1**	**1[a]**	**29**	**85**	**every 12 weeks up to week 85**	**every 24 weeks from week 85**	**Safety FU**
Week		**1**	**5**	**13**			**30 days after last dose of MDV 3100**
Window (days)		**NA**	**± 3**	**± 7**	**± 7**	**± 7**	**± 7**
Informed Consent	X[b]						
Inclusion/Exclusion Criteria		X					
Medical History		X					
Vital Signs[c]		X	X	X	X	X	X
Physical Examination		X	X	X	X	X	X
Weight		X	X	X	X	X	X
12-lead ECG		X	X	X	X	X	X
Clinical laboratory tests[d]		X	X	X	X	X	X
ECOG Performance Status		X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X
MDV3100 Dispensing		X	X	X	X	X	

a. The final visit of the prior study with MDV3100 in which the subject is taking study drug and all assessments done during this visit, will serve as the initial visit (day 1) and visit assessments for this extension study.

b. To ensure that MDV3100 is taken continuously without interruption, the subjects will be informed about the extension study at any of the visits during the previous study and sign ICF prior to visit on day 1 of this study.

c. Vital signs (blood pressure, pulse rate, respiration rate, and temperature) will be obtained prior to study drug administration.

d. Clinical laboratory tests, hematology and chemistry, will be obtained prior to study drug administration.

3 STUDY OBJECTIVE(S), DESIGN

3.1 Study Objectives

The main objective of this study is to follow up the long-term safety of continued administration of MDV3100 in prostate cancer subjects who were enrolled and completed MDV3100 treatment period in prior (e.g., phase 1) studies.

The long-term safety will be determined by:

- Adverse Events
- Vital Signs
- 12-lead ECGs
- Physical Examination
- Safety laboratory evaluation
- ECOG performance status.

3.2 Study Design

This is a multi-center phase 2, open-label extension study in prostate cancer subjects who have completed MDV3100 treatment in a prior study. In order to participate in this study, the subjects must have completed the prior study with MDV 3100, be in the state of at least stable disease and in the opinion of the investigator would derive benefit from continuing MDV3100 treatment. The final visit in the prior MDV3100 study, in which the subject is taking study drug, will serve as the initial visit for this extension study.

The extension protocol's baseline, for comparison purposes, will be a baseline from the prior MDV3100 study. In addition, all ongoing concomitant medications and AEs from the prior study will be transferred onto the appropriate case report forms (eCRFs) for this study.

All subjects will take 160 mg (4 capsules) MDV3100 once daily oral dose at the same time each day. MDV3100 can be taken with or without food.

Subjects will be discontinued from study drug when continued administration of study drug is deemed to be not in the subject's best interest by the investigator based on clinical assessments. Use of other investigational drugs will also lead to discontinuation.

Throughout the study, safety and tolerability will be assessed by the recording of AEs, monitoring of vital signs and physical examinations, safety laboratory evaluations, and 12-lead electrocardiograms (ECGs).

Subjects will have a safety follow-up visit 30 days after their last dose of study drug.

3.3 Assignment and Allocation

Subjects will be assigned to a subject number at study entry (signing of Informed Consent Form).

3.4 Transfer of data from prior study

Relevant data from the prior study has been transcribed to the eCRF of this study. This is done on the basis of specific instructions by the Investigators involved.

Demographic information (date of birth, ethnicity, race as described by the subject and height) collected at screening of the prior study with MDV3100 has been transcribed onto the appropriate eCRF for this study.

Medical history, as well as non prostate cancer medical history that stopped at or prior to screening, recorded at screening of the prior study with MDV3100 has been transcribed onto the appropriate eCRF for this study.

Medical history and disesase history of the target disease recorded at screening of the prior study with MDV3100 has been transcribed onto the appropriate eCRF for this study.

As stated earlier, in addition, all ongoing concomitant medications (including non-medication therapies) and AEs from the prior study have been transferred onto the appropriate case report forms (eCRFs) for this study.

Further details can be found in the Investigators EDC Instruction Manual (see references).

Because of the transfer of all relevant data from the prior study, the reporting of the extension study will be exclusively based on the data available in the database of this extension study. The only exception is that for a number of safety assessments (Laboratory data, Vital signs, ECG data and the ECOG scale) as baseline the last assessment before the first MDV3100 intake of the prior study will be used.

4 SAMPLE SIZE

Subjects who were actively enrolled and have completed MDV3100 treatment in prior named studies, are eligible to participate in this study when continuation of MDV3100 is deemed by the investigator in the best interest of the subjects. There is no statistically determined sample size for this safety follow up study.

5 ANALYSIS SETS

In accordance with ICH recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

5.1 Safety Analysis Set (SAF)

Only one analysis set is defined for this study. The Safety Analysis Set (SAF) is defined as all subjects who have taken at least one dose of study drug in this extension study.

6 ANALYSIS VARIABLES

6.1 Efficacy Variables

Not applicable.

6.2 Safety Variables

Safety will be assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs; frequency, seriousness, severity (NCI-CTCAE grade) and relationship to study drug)
- Safety laboratory variables (hematology and biochemistry)
- Vital signs (blood pressure, pulse rate, respiration rate, temperature and body weight)
- Physical examination
- 12-lead electrocardiogram (ECG)

TEAE: An adverse event observed after starting administration of study drug during the extension study. If a subject experiences an event during the prior study with MDV3100 which continues during this extension study, the event will be considered as TEAE only if it has worsened in severity (i.e. it is reported with a new start date during the extension period) All adverse events collected that begin within 30 days of taking the last dose of study drug will also be counted as TEAE.

6.3 Pharmacokinetics

No PK assessment involved.

7 STATISTICAL METHODOLOGY

7.1 General Considerations

No inferential statistical analyses will be conducted. Descriptive statistics including the number of subjects (n), mean, standard deviation (SD), median, minimum and maximum will be used to summarize continuous variables. Number (n) and percentage (%) of subjects in each category will be used to summarize categorical variables. All data processing, summarization, and analyses will be performed using SAS® Version 9.1 or higher on Unix. Specifications for table, graphs and data listing formats can be found in the TLF specifications for this study.

7.2 Study Population

7.2.1 Disposition of Subjects

The subject disposition will be summarized and presented for the safety analysis set (SAF):

- Number and percentage of subjects enrolled in study;
- Number and percentage of subjects who stayed on study medication for the complete duration of the study* or discontinued from the study by reason of discontinuation.

  *this extension study is open ended in the sense that no maximum duration is defined. The study will end when all subjects on medication have discontinued treatment or the sponsor makes the decision to terminate the study.

7.2.2 Protocol Deviations

Protocol deviations will be assessed for all subjects allocated to treatment.

The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall, by total as well as by study site. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one protocol deviation will be counted once in the overall summary. A data listing will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

7.2.3 Demographics and Other Baseline Characteristics

Descriptive summary statistics will be produced for all parameters. For the calculation of age the initial visit of the extension study (Day 1) will be used as the reference date. For weight and BMI the data assessed at the baseline of the prior study will be used.

Demographic data and other baseline characteristics will be provided in a listing.

7.2.4 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be obtained at screening visit (see section 3.4).

Non-prostate cancer related medical history data will be summarized by presenting the number and percentage on the SAF. The summary table will be presented alphabetically by system organ class and by decreasing order of frequency of preferred terms within each system organ class.

Cancer history will be summarized by presenting the number and percentage of subjects for tumor and lymph node stages, Gleason scores, incidence of metastases and previous therapies on the FAS. The duration of prostate cancer will be calculated as (Date of first MDV3100 intake in the prior study – Date of Initial Diagnosis) + 1. Descriptive statistics will be used to summarize the duration of disease.

A listing of medical history will be provided.

7.2.5 Concomitant Medications

Concomitant medications (prescription, over-the-counter, and nutritional supplements) will be coded using the World Health Organization (WHO) drug dictionary and will be summarized by preferred WHO name and reported term. Medications will be counted by the number of subjects who took each medication. A subject taking the same medication multiple

times will only be counted once for that medication. Medications will be presented in decreasing order of frequency based on the total number of subjects who took each medication.

All concomitant medication data will be provided in a listing.

Concomitant medications are those medications or therapies with at least one dose taken between the date of first MDV3100 intake in the 121 study (inclusive) and the date of last MDV3100 dose (inclusive) and up to the end of the study.

7.3 Study Drug

Duration of treatment and total dose will be summarized in two ways:

- Descriptive statistics of MDV3100 exposure in Days
- Exposure time will be categorized according to the following categories:
  - <2 months
  - ≥2 – <6 months*
  - ≥6 – <12 months*
  - ≥12 months

*The following convention will be applied: 2 months = 60 days; 6 months = 180 days and 12 months = 365 days.

Counts and percentage of subjects in each of these categories will be summarized.

The duration of exposure (number of days) to study medication will be summarized using descriptive statistics on the SAF, where the duration of exposure to MDV3100 is defined as the last known date that subject took MDV3100 during this study – the first dose date in this study + 1 day. Dose interruptions will be ignored in the calculation.

Also a summary of average daily dose during the extension period will be provided. The daily dose received by a subject is collected for each CRF visit. Changes in dose are also collected. The daily dose will be assumed the same between 2 CRF visits if no change in dose is recorded.

In addition information on MDV3100 compliance will be summarized via descriptive statistics and via categories (<80%, ≥80%). Percentage compliance is defined as the total number of capsules taken divivded by the total number of capsules that should have be taken:

$$\frac{\text{[Total number of tablets consumed]}}{\text{[('Date last dose of study drug' - 'Date first dose') + 1] * 4}} \times 100$$

where, total number of capsules consumed will be calculated as:
(total number of capsules dispensed) – (total number of capsules returned).

All study drug dosing information will be provided in a listing

7.4 Analysis of Efficacy

Not applicable

7.5 Analysis of Safety

Safety analyses will be conducted using the SAF.

7.5.1 Adverse Events

AEs will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Authorities (MedDRA) and graded using NCI-CTCAE.

Treatment-emergent adverse events (TEAE) will be presented within each system organ class by preferred term, by relationship to study drug and by severity (NCI-CTCAE grade). AEs leading to dose reduction or temporary discontinuation of study drug, AEs leading to permanent discontinuation of study drug, SAEs, and SAEs by NCI-CTCAE grade will be summarized. AEs will also be summarized by NCI-CTCAE grade and relationship to study drug jointly.

All AEs data will be displayed in listings. In addition listings of deaths, SAEs, drug related AEs, AEs leading to dose reduction or temporary discontinuation of study drug and AEs leading to permanent discontinuation of study drug will be presented.

7.5.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations (including hematology and serum chemistry) will be summarized for each visit using descriptive statistics. Change from baseline will also be summarized. As a baseline the last assessment before the first day of MDV3100 intake from the prior study will be used. Shift analysis tables will present shift from baseline to the same visits using the NCI-CTCAE grade and laboratory reference range indicator. All clinically significant abnormal laboratory values will be recorded as AEs and graded using NCI-CTCAE guidelines.

Laboratory data will be listed for each test. Each laboratory result will be flagged as low (L), normal, or high (H) at each visit according to laboratory reference ranges. In addition a listing will be presented with the indicated subset of laboratory parameters, if at least one of the following criteria is fulfilled: ALT or AST >= 3xULN or Bilirubin >= 2.0 mg/dL (34.2 µmol/L) or Creatinine > 352 µmol/L (4.0 mg/dL).

7.5.3 Physical Examination

All clinically significant abnormal findings will be recorded as medical history or AEs and graded using NCI-CTCAE guidelines.

7.5.4 Vital Signs

Descriptive statistics will be presented for each vital sign measurement at each visit. Change from baseline will also be summarized. In addition for weight a frequency table indicating percentage change from baseline by category* will be provided. As a baseline the last assessment before the first day of MDV3100 intake from the prior study will be used.

Vital signs data will be provided in a data listing.

*The percentage change will be categorized in 7 different categories, from loss >=20% up to gain >=20% (see TLF specifications for the other categories)

7.5.5 Electrocardiogram (ECG)

Overall ECG interpretation will be summarized for each visit. A shift analysis table showing shifts from baseline to each visit in overall ECG interpretation (normal, abnormal not clinically significant, and abnormal clinically significant) will be provided. As a baseline the last assessment before the first day of MDV3100 intake from the prior study will be used.

ECG data will be provided in a data listing.

7.6 Analysis of Pharmacokinetics

Not applicable.

7.7 Other Analyses

The Eastern Cooperative Oncology Group (ECOG) scale categorized as grade scores 0-5 will be used to assess performance status. The higher grade score of ECOG indicates the worse of the patient's performance. Number and percentage of subjects with grade scores 0-5 will be tabulated at scheduled visits. A shift analysis table showing shifts from baseline to each scheduled visit in ECOG PS grade will be provided. In addition a shift analysis table showing shift from baseline to the highest ECOG PS grade during the extension study will be provided. As a baseline the last assessment before the first day of MDV3100 intake from the prior study will be used.

The ECOG performance status will be provided in a data listing

7.8 Interim Analysis (and Early Discontinuation of the Clinical Study)

Not applicable

7.9 Handling of Missing Data, Outliers, Visit Windows, and Other Information

7.9.1 Missing Data

As a general principle, no imputations of missing data will be done. Exceptions are the following:

- Partially missing date of initial diagnosis will be imputed to get the duration of prostate cancer. For an incomplete initial diagnosis date, the first day of the month and/or the 1st month of the year will be used.
- The worst case scenario will be used in the estimation of partial dates for adverse events and concomitant medication. That is, for an incomplete start date the first day of the month or the first month of the year will be used (unless this leads to an estimated date before the date of first dose of study drug, which will be used in these cases) and for an incomplete stop date the last day of the month or the last month of the year will be used in order to assess whether an adverse event should be analyzed

as a TEAE or whether a medication should be analyzed as concomitant medication. Completely missing start or stop dates will not be estimated. Adverse events or medications with completely missing start date will be assumed to be non TEAEs or not concomitant, respectively. Any stop date that is derived to be after death date or last observed date in the study (e.g. date of lost to follow up) will be set to the date of death or last observed date, respectively. The corresponding listings will always show the original date and time information.

7.9.2 Visit Windows

Visit windows are allowed for certain visits per the schedule of assessments. Subject data will not be excluded from analyses due to the subject's failure to comply with the visit schedule. The visit windows for safety variables are described in the following table.

Table 2 Analysis visit window

Visit day interval	Scheduled visit	Analysis visit
Baseline	Baseline prior study	Baseline
Day 1*	Week 1	Day 1
Day 2 – Day 57	Week 5	Week 5 (Day 29)
Day 58 – Day 127	Week 13	Week 13 (Day 85)
Day 128 – Day 211	Week 25	Week 25 (Day 169)
Day 212 – Day 295	Week 37	Week 37 (Day 253)
Day 296 – Day 379	Week 49	Week 49 (Day 337)
Day 380 – Day 463	Week 61	Week 61 (Day 421)
Day 464 – Day 547	Week 73	Week 73 (Day 505)
Day 548 – Day 673	Week 85	Week 85 (Day 589)
Day 674 – Day 841	Week 109	Week 109 (Day 757)
Day 842 – Day 1009	Week 133	Week 133 (Day 925)
Similarly for follow-up visits		

*Day 1 of extension; all day numbers are relative to day 1 of the extension study

In the case of multiple observations at a specific visit, the observation which is closest to the target date will be used. If the observations have the same distance to the target visit, the latest one will be used.

All visit dates and times of dosing will be provided in a listing for each study period.

8 REFERENCES

ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics)

Investigators EDC Instruction Manual for protocol 9785-CL-0121; Internal Astellas document

9 APPENDICES

9.1 Appendix 1: Signatures

(E-signatures are attached at end of document)

Prepared by: _____ Date: _____

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