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

ISN/Protocol 9785-CL-0121

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Sponsor: Astellas Pharma Europe B.V. (APEB)

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The Netherlands

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Protocol for Phase 2 Study of MDV3100

ISN/Protocol 9785-CL-0121

Version 5.0

Incorporating Substantial Amendment 4 [See Attachment 1]

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I. SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g., protocol authors, sponsor's reviewers and contributors) are located in Section 14. Sponsor's Signatures; e-signatures (when applicable) are located at the end of this document.

2. INVESTIGATOR'S SIGNATURE

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

ISN/ Protocol 9785-CL-0121 / Version 5.0

Incorporating Substantial Amendment 4 / 20 June 2016

I have read all pages of this clinical study protocol for which Astellas is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: .....

Date (DD MMM YYYY)

Printed Name: .....

Address: .....

.....

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) **See Section 0**	**Astellas Pharma Global Development** **Product Safety and Pharmacovigilance** **Telephone:** [redacted] **Fax:** [redacted] **Email:** [redacted]
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III. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of Abbreviations
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APEB	Astellas Pharma Europe BV
APGD	Astellas Pharma Global Development
AR	Androgen Receptor
AST	Aspartate Aminotransferase
AT	Aminotransferase
BUN	Blood Urea Nitrogen
CA	Competent Authorities
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CO_2	Bicarbonate
CRO	Contract Research Organization
CRPC	Castration-resistant prostate cancer
CYP	Cytochrome P450
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic Acid
EU	European Union
FDA	Food and Drug Administration
FU	Follow up
GnRH	Gonadotropin-releasing hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GMP	Good Manufacturing Practice
HCT	Hematocrit
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
IRB	Institutional Review Board
ISN	International Study Number
LA-CRF	Liver Abnormality Case Report Form
LFT	Liver Function Tests

Abbreviations	Description of Abbreviations
LHRH	Luteinizing Hormone Releasing Hormone
MedDRA	Medical Dictionary for Regulatory Activities
MDV3100	3-(4-cyano-3-trifluoromethylphenyl)-1-[3-fluoro-4-(methylcarbamoyl)phenyl]-5,5-dimethyl-2-thioxoimidazolin-4-one
MAA	Marketing Authorization Application
NASH	Non-alcoholic Steato Hepatitis
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
PB	Privacy Board
PFS	Progression-free survival
P-gp	P-glycoprotein
PHI	Protected Health Information
PK	Pharmacokinetics
PSA	Prostate-specific antigen
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SOP	Standard Operating Procedure
TBL	Total Bilirubin
$t_{1/2}$	Apparent Terminal Elimination Half-life
ULN	Upper Limit of Normal
WBC	White Blood Cell

List of Key Study Terms

Terms	Definition of terms
Baseline	1) Observed values/findings which are regarded as calibrated zero status in the present study, 2) Time when 'Baseline' is observed.
Discontinuation	The act of concluding participation, prior to completion of all protocol-required elements, in a trial by an enrolled subject. Four categories of discontinuation are distinguished: a) dropout: Active discontinuation by a subject (also a noun referring to such a discontinued subject); b) investigator-initiated discontinuation (e.g., for cause); c) loss to follow-up: cessation of participation without notice or action by the subject; d) sponsor-initiated discontinuation. Note that subject discontinuation does not necessarily imply exclusion of subject data from analysis. "Termination" has a history of synonymous use, but is now considered non-standard.
Enroll	To register or enter into a clinical study; transitive and intransitive. Informed consent precedes enrollment, which precedes or is contemporaneous with treatment allocation.
End of study	The end of study for this protocol is defined as Last Subject's Last Visit.
Investigational Period	Period of time where major interests of protocol objectives are observed, and where the study drug or comparative drug is given to a subject, and continues until the last assessment after completing administration of the study drug or comparative drug.
Screening	1) Process for retrieving candidates for the study. 2) Process for checking the eligibility of subjects done prior to the investigational period.
Study Drug	Agents given as part of a clinical trial. In this study, MDV3100 is the study drug.
Study Period	Period of time beginning with the first subject consented through to the last observation collected for the study.
Subject	An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Title of Study	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 [ISN 9785-CL-0121]
Planned Study Period	From 3Q2011 to 1Q2017
Study Objective(s)	Primary Objective: 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 a prior study with MDV3100.
Planned Total Number of Study Centers and Location	Those sites that currently have subjects actively enrolled and completed MDV3100 treatment in a prior study with MDV3100 may participate.
Design and Methodology	This is a multi-center phase 2 open-label extension study in subjects with prostate cancer who have completed MDV3100 treatment in a previous study with MDV3100 to assess the long-term safety of continued administration of MDV3100, when judged by the investigator to be in the best interest of the subject. For the study duration, all subjects with castration-resistant prostate cancer (CRPC) will have to maintain androgen deprivation with an LHRH agonist/antagonist unless they underwent bilateral orchiectomy. 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 assessment. Throughout the study, safety and tolerability will be assessed by the recording of adverse events, monitoring of vital signs and physical examinations, safety laboratory evaluations, and 12-lead electrocardiograms (ECGs). Subjects that have not met any of the discontinuation criteria as outlined in Section 3.4 may be eligible to continue to receive treatment with enzalutamide in Study [redacted] upon approval and activation of this study at the participating institution. Subjects who enroll in Study [redacted] will not be required to have a safety follow-up visit. Subjects who choose not to participate or are not eligible for Study [redacted] will complete their participation in Study 9785-CL-0121 by completing the safety follow-up visit upon activation of Study [redacted] at the institution.
Number of Subjects Planned	Subjects who were actively enrolled and have completed MDV3100 treatment in a previous study with MDV3100 may be eligible to participate in this study when continuation of MDV3100 is deemed by the investigator in the best interest of the subjects.

Selection Criteria	Inclusion Criteria: Subject is eligible for the study if all of the following apply: 1. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable). 2. Has completed a prior study with MDV3100, can be enrolled in this extension study without any interruption in study drug and in the opinion of the investigator would derive benefit from continuing MDV3100 treatment. 3. No new clinically significant abnormalities based upon physical examination, safety laboratory data, vital signs, ECG, and other clinical assessments noted from the last visit conducted during the subject's active MDV3100 study prior to initiation of this study. 4. Male subjects and their female spouses/partners who are of childbearing potential must be using highly effective contraception[1] consisting of two forms of birth control (one of which must be a barrier method) starting at Screening and continue throughout the study period and for 3 months after final study drug administration. Male subjects must not donate sperm starting at Screening and throughout the study period and for at least 3 months after final study drug administration. [1]Highly effective contraception is defined as: • Established use of oral, injected or implanted hormonal methods of contraception. • Placement of an intrauterine device (IUD) or intrauterine system (IUS). • Barrier methods of contraception: Condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal form/gel/film/ cream/suppository 5. Subject agrees not to participate in another interventional study while on treatment. Exclusion Criteria: Subject will be excluded from participation if any of the following apply: 1. Subject has a history of seizure or any condition that may predispose to seizure including, but not limited to underlying brain injury, stroke, primary brain tumours, brain metastases, or alcoholism. 2. Subject has a history of loss of consciousness or transient ischemic attack within 12 months prior to Day 1 of the completed preceding study. 3. Use of the following prohibited medication/therapies: • Concomitant medication that likely could cause clinically relevant drug-to-drug interactions with MDV3100. • Other (than MDV3100) androgen-receptor (AR) antagonists (bicalutamide, flutamide, nilutamide). • Investigational therapy other than MDV3100 or investigational procedures of any kind.

Discontinuation Criteria	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 assessment. Use of other investigational drugs will also lead to discontinuation. It is also possible that the sponsor or the competent authorities (CA) request termination of the study if there are concerns about conduct or safety. Astellas will be closing Study 9785-CL-0121. Subjects that have not met any of the discontinuation criteria as outlined in Section 3.4 may be eligible to continue to receive treatment with enzalutamide in Study [redacted] upon approval and activation of this study at the participating institution. Subjects who choose not to participate or are not eligible for Study [redacted] will complete their participation in Study 9785-CL-0121 by completing the safety follow-up visit upon activation of Study [redacted] at the institution.
Test Drug Dose: **Mode of Administration:** **Duration of Treatment:**	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 receive their assigned therapy until discontinuation criteria are met.
Reference Therapy Dose:	Not applicable
Concomitant Medication	The following medications are prohibited while the subject is continuing on study drug: • Concomitant medication that likely could cause clinically relevant drug-to-drug interactions with MDV3100 • Other than MDV3100 AR antagonists (bicalutamide, flutamide, nilutamide) • Investigational therapy other than MDV3100 or investigational procedures of any kind. When applicable, the following medications should be maintained during the investigational period at the same dosage and schedule: • LHRH agonist/antagonist. Co-administration of a strong CYP2C8 inhibitor (e.g., gemfibrozil) increased the composite AUC0-inf of MDV3100 plus its active metabolite in healthy volunteers; therefore, co-administration of MDV3100 with strong CYP2C8 inhibitors should be avoided, if possible. The effects of CYP2C8 inducers on the PK of MDV3100 have not been evaluated in vivo. Co-administration of MDV3100 with strong or moderate CYP2C8 inducers (e.g., rifampin) may decrease the plasma exposure of MDV3100 and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP2C8 induction potential is recommended. Co-administration of MDV3100 with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may decrease the plasma exposure of MDV3100 and should be avoided, if possible.

	Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended. Moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) and St John's Wort may also reduce the plasma exposure of MDV3100 and should be avoided, if possible. MDV3100 is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. Concomitant use of MDV3100 with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided, as MDV3100 may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.
Primary Variable	Safety parameters include clinical laboratory test, 12-lead ECGs, vital signs, physical examination and adverse events (AEs).
Secondary Variable	Not applicable
Statistical Methods	No formal statistical analysis will be conducted. Descriptive summary statistics will be produced.

V. SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments

Study Day	-32 to -1	1[a]	29	85	every 12 weeks up to week 85	every 24[d] weeks from week 85	Safety FU[e, f]
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		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	

Footnotes

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. If the subject is eligible to continue in extension Study [redacted], the final visit of Study 9785-CL-0121 will serve as the initial visit (day 1) for extension Study [redacted]. Subjects who enroll in Study [redacted] will not be required to have a safety follow-up visit.

e. If a new cytotoxic or investigational anticancer treatment is initiated before 30 days after last dose, then safety follow-up for Study 9785-CL-0121 should occur immediately before starting the new treatment.

f. Subjects who choose not to participate or are not eligible for Study [redacted] will complete their participation in Study 9785-CL-0121 by completing the safety follow-up visit upon activation of Study [redacted] at the institution.

1 INTRODUCTION

1.1 Background

Enzalutamide is approved in the US, Canada and EU for patients with metastatic CRPC who have previously received docetaxel. Enzalutamide (formerly MDV3100) is an androgen receptor (AR) inhibitor that blocks multiple steps in the AR signaling pathway. Enzalutamide competitively inhibits binding of androgens to ARs, inhibits nuclear translocation of receptors and inhibits the association of the AR with DNA even in the setting of AR over expression and in prostate cancer cells resistant to anti-androgens. By inhibiting AR signaling, enzalutamide elicits several downstream effects, which include reduced expression of AR-dependent genes, decreased growth of prostate cancer cells, induction of cancer cell death, and tumor regression. Enzalutamide lacks agonist activities such as those that may limit the sustained efficacy of current anti-androgens.

The 9785-CL-0121 study is an extension to the preceding MDV3100 studies offering patients a possibility to continue MDV3100 medication if deemed as being of benefit to the patient by the investigator. 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.

1.2 Non-clinical and Clinical Data

1.2.1 Non-clinical Data

In mice, rats, and dogs, oral MDV3100 had a half-life ($t_{1/2}$) of approximately 0.25 to 3 days. The $t_{1/2}$ did not appear to be affected by the dose size; however, the bioavailability appeared to decrease with increasing dose size. Plasma protein binding of MDV3100 in human plasma ranged from 97.2% to 97.8% and was similar in mice, rats, rabbits, and dogs. In vitro drug metabolism studies suggest that MDV3100 undergoes very slow rates of metabolism. In vitro drug metabolism studies suggest that MDV3100 may have the potential to induce cytochrome P450 (CYP) 3A4 and to directly inhibit CYP2B6, CYP2C8, CYP2C9, and CYP2C19. In consideration of time-dependent inhibition data, a metabolite of MDV3100 may inhibit CYP1A2 [Investigator's Brochure].

1.2.2 Clinical Data

A clinical drug-drug interaction study in 41 healthy volunteers (9785-CL-0006) revealed that CYP2C8 plays an important role in the elimination of MDV3100 and the formation of the active metabolite. Following oral administration of the strong CYP2C8 inhibitor gemfibrozil (600 mg twice daily) to healthy male subjects the AUC of MDV3100 increased 4.26-fold, while Cmax decreased by 18%; the AUC and Cmax of the active metabolite decreased by 25% and 44% respectively. CYP3A4 plays a minor role in the metabolism of MDV3100. Following oral administration of CYP3A4 inhibitor itraconazole (200 mg once daily), the AUC of MDV3100 increased by 1.41-fold while the Cmax was essentially unaffected (decreased by 2%); the AUC of the active metabolite increased 1.21-fold while the C_{max} decreased by 14%.

A clinical drug-drug interaction study in 14 patients with castration resistant prostate cancer (9785-CL-0007) indicated that MDV3100 (160 mg once daily to steady state) has no clinically relevant effect on CYP2C8, is a moderate inducer of CYP2C19 and CYP2C19, and is a strong inducer of CYP3A4, based on changes in plasma AUC0-inf for single doses of the sensitive substrates pioglitazone, S-warfarin, omeprazole and midazolam respectively.

The PK of MDV3100 were examined in subjects with baseline mile (n=6) or moderate (n=8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 14 matched control subjects with normal hepatic function (9785-CL-0009). Following a single 160 mg dose of MDV3100, exposure parameters of MDV3100 increased by approximately 24% and 29% in subject with mild and moderate hepatic impairment, respectively, compared to healthy control subjects. Hepatic impairment had similar minimal effects on the exposure parameters of the active metabolite.

A total of 1199 subjects were enrolled in a phase 3 randomized, double-blind, placebo-controlled study in patients with progressive castration resistant prostate cancer previously treatment with docetaxel-based chemotherapy (CRPC2/AFFIRM). The protocol pre-specified interim analysis after 520 deaths showed a statistically significant superiority in overall survival in patients treated with MDV3100 compared to placebo. Interim data revealed that the estimated median overall survival in man who had received MDV3100 was about 18.4 months compared with 13.6 months for the placebo group. An overall survival difference of 4.8 months and a 37% reduction of risk of death were observed. This benefit was sufficiently compelling to stop the patient study early and switch men who had taken placebo over to MDV3100.

Please see the most current version of the IB for additional details.

1.3 Summary of Key Safety Information for Study Drugs

More than 4900 subjects and patients have been enrolled worldwide in completed and ongoing clinical trials evaluating enzalutamide of whom, approximately 3200 received at least 1 dose of enzalutamide (MDV3100).

In the phase 3 study CRPC2 (AFFIRM; N = 1199), a randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide (160 mg daily) in patients with progressive CRPC previously treated with docetaxel-based chemotherapy, the most common adverse drug reactions (³ 5%) in patients treated with enzalutamide (N = 800) were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. Discontinuations due to adverse events were reported for 16% of enzalutamide-treated patients and 18% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the enzalutamide-treated patients and none (0%) of the placebo-treated patients.

In the phase 3 study MDV3100-03 (PREVAIL; N = 1717), a multinational, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide in chemotherapy-naïve patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy, enzalutamide was generally well tolerated with an overall safety profile consistent with that observed in AFFIRM, with a lower seizure rate observed in PREVAIL (1 patient [0.1%] each in the enzalutamide and placebo treatment groups).

Additional information on the clinical experience with enzalutamide is provided in the most current edition of the MDV3100 Investigator's Brochure.

1.4 Risk-Benefit Assessment

MDV3100 is a novel small molecule designed to have an increased affinity for the androgen receptor and more effective suppression of the androgen pathway in the setting of androgen over expression [Tran et al, 2009]. MDV3100 has a higher binding affinity to the AR (8-10 times greater), has no agonist activity, and has demonstrated superior AR downstream effects compared to bicalutamide in pre-clinical studies. In a clinical trial (phase 1-2) involving 140 castrate subjects with progressive prostate cancer who have either failed androgen deprivation therapy or chemotherapy, MDV3100 has shown strong anti-tumor effects. These effects include reduction of PSA, prolonged time to radiographic and PSA progression and CTC conversion from unfavorable to favorable status.

Commonly used androgen receptor antagonists are flutamide, bicalutamide and nilutamide. The endocrine effects of antiandrogens usually include significant increases in LH, Follicle Stimulating Hormones, Testosterone and Estradiol .Common adverse effects resulting from androgen receptor blockade are to be expected. For these compounds the most common side effects are known and include breast pain, gynecomastia, hot flushes, back pain, asthenia, and constipation.

It has now been shown in phase1-3 clinical trials that MDV3100 demonstrates a similar endocrine response profile (hypergonado-tropic hypergonadism) as other marketed AR antagonists. Given the strong in vitro data showing superiority to bicalutamide, the nonclinical data demonstrating few toxicities, robust clinical data from the phase 1-3 showing anti-tumor effect, the favorable overall safety profile of MDV3100 in the phase 1-3 completed and ongoing studies, together with the manageable safety profile , the benefits of studying MDV3100 outweigh the risks involved. Patients with locally advanced or metastatic prostate cancer may benefit from a compound that offers improved efficacy to traditional anti-androgens coupled with a less unfavorable side effect profile when compared to LHRH analogues. The proposed total daily dosage (160 mg) in the proposed study seems to be acceptable in light of the safety and efficacy data obtained to date. The identified risk of seizure and potential risks described for currently approved anti-androgens will be monitored through clinical follow-up and by routine laboratory assessments. The FDA's guidance for Drug-Induced Liver Injury (DILI) will also be followed. In summary, the benefit risk profile for patients participating in the study that will be treated with MDV3100 is considered to be favorable as potential benefits exceed identified and potential risks. Please refer to the most

current edition of the MDV3100 Investigator's Brochure for complete information on risk/benefit.

The 9785-CL-0121 is an extension study to prior MDV3100 studies and subjects will only participate in this extension study if they have been actively enrolled and have completed MDV3100 treatment in the prior MDV3100 study and when administration of MDV3100 is deemed by the investigator/treating physician to be in the patient's best interest. Routine subject disease management will assess the risks and benefits of the continued use of MDV3100. The possibility of offering patients who benefit from MDV3100 in the preceding study continuous medication within the boundaries of an extension study is in compliance with the ethical principles for oncology phase 1 studies.

2 STUDY OBJECTIVE(S), DESIGN AND ENDPOINTS

2.1 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.

2.2 Study Design and Dose Rationale

2.2.1 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 MDV3100 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.

This protocol's baseline, for comparison purposes, will be considered the original baseline from the previous MDV3100 study. In addition, all ongoing concomitant medications and AEs from the previous 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 that have not met any of the discontinuation criteria as outlined in Section 3.4 may be eligible to continue to receive treatment with enzalutamide in Study [redacted] upon approval and activation of this study at the participating institution. Subjects who enroll in Study [redacted] will not be required to have a safety follow-up visit.

Subjects who choose not to participate or are not eligible for Study [redacted] will complete their participation in Study 9785-CL-0121 by completing the safety follow-up visit upon activation of Study [redacted] at the institution.

See Section V, Table 1, Schedule of Assessments for an outline of study procedures.

2.2.2 Dose Rationale

Subjects enrolled into this extension study will continue to receive 160 mg/day of MDV3100 until the investigator and/or sponsor feels that continued use of MDV3100 is not beneficial to the subject, or the subject withdraws consent.

2.3 Endpoints

2.3.1 Primary Endpoints

Safety, as measured by adverse events, vital signs, 12-lead ECGs, physical examination and safety laboratory evaluation.

2.3.2 Secondary Endpoints

Not applicable.

2.3.3 Exploratory Endpoints

Not applicable.

3 STUDY POPULATION

3.1 Selection of Study Population

Subjects actively enrolled and completed MDV3100 treatment in prior studies, are eligible to participate in this study.

3.2 Inclusion Criteria

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Has completed a prior study with MDV3100, can be enrolled in this extension study without any interruption in study drug, and in the opinion of the investigator would derive benefit from continuing MDV3100 treatment.
3. No new clinically significant abnormalities based upon physical examination, safety laboratory data, vital signs, ECG, and other clinical assessments noted from the last visit conducted during the subject's active MDV3100 study prior to initiation of this study.
4. Male subjects and their female spouses/partners who are of childbearing potential must be using highly effective contraception[1] consisting of two forms of birth control (one of which must be a barrier method) starting at Screening and continue throughout the study period and for 3 months after final study drug administration. Male subjects must not donate sperm starting at Screening and throughout the study period and for at least 3 months after final study drug administration.
5. Subject agrees not to participate in another interventional study while on treatment.

[1]Highly effective contraception is defined as:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: Condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal form/gel/film/cream/suppository

Waivers to the inclusion criteria will **NOT** be allowed**.**

3.3 Exclusion Criteria

Subject will be excluded from participation if any of the following apply:

1. Subject has a history of seizure or any condition that may predispose to seizure including, but not limited to underlying brain injury, stroke, primary brain tumours, brain metastases, or alcoholism.
2. Subject has a history of loss of consciousness or transient ischemic attack within 12 months prior to Day 1 of the completed preceding study.
3. Use of the following prohibited medication/therapies:
    - Concomitant medication that likely could cause clinical relevant drug-to-drug interactions with MDV3100
    - Other (than MDV3100) androgen-receptor antagonists (bicalutamide, flutamide, nilutamide)
    - Investigational therapy other than MDV3100 or investigational procedures of any kind.

Waivers to the exclusion criteria will **NOT** be allowed.

3.4 Discontinuation Criteria for Individual Subjects

A discontinuation is a subject who enrolled in the study and for whom study drug is terminated for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

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. It is also possible that the sponsor or the competent authorities (CA) request termination of the study if there are concerns about conduct or safety.

Unless the subject withdraws consent, all subjects discontinuing study drug for any reason will have a safety follow-up visit 30 days after their last dose of MDV3100. For subjects who enroll into Study [redacted], a safety follow-up visit is not required. For these subjects, the final visit for Study 9785-CL-0121 will serve as Day 1 for Study [redacted] (±7 days).

Individual subjects may discontinue the study in case of:

1. Not fulfilling inclusion or exclusion criteria
2. Adverse event
3. Lack of efficacy
4. Withdrawal of consent
5. Subject lost to follow-up
6. Protocol violation.

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 MDV3100 (Enzalutamide)

MDV3100 has the chemical name 3-(4-cyano-3-trifluoromethylphenyl)-1-[3-fluoro-4-(methylcarbamoyl) phenyl]-5, 5-dimethyl-2-thioxoimidazolin-4-one.It is a white to off-white solid that is insoluble in water and no salt forms are available at approximately pH 2 to 10.

The drug substance is formulated in the surfactant, Labrasol, to create a self-emulsifying (or microemulsifying) dosage form. The product will be supplied as liquid-filled soft gelatin capsules containing 40 mg of MDV3100.

4.1.2 Comparative Drug(s)

Not applicable.

4.2 Packaging and Labeling

All medication used in this study will be prepared, packaged, and labeled under the responsibility of a qualified person (QP) at Astellas Pharma Europe BV (APEB) or at sponsor's designee in accordance with APEB or sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonization for Good Clinical Practice (ICH GCP) guidelines, and applicable local laws/regulations.

The Investigational Medicinal Product (IMP) will be labeled according to the requirements as published in Annex 13 of the GMP guidelines and/or local requirements. The labels will be approved by a local representative and finally released by the head of quality control or sponsor's designee. A Qualified Person (from APEB) or sponsor's designee will release the final IMP according to the requirements of EU Directive 2003/94/EG and/or local laws/regulations.

4.3 Study Drug Handling

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by a responsible person (e.g., pharmacist), and

- that such deliveries are recorded
- that study drug is handled and stored safely and properly
- that study drug is only dispensed to study subjects in accordance with the protocol
- that any unused study drug is returned to the sponsor or standard procedures for the alternative disposition of unused study drug are followed.

Drug inventory and accountability records for the study drugs will be kept by the investigator/ pharmacist. Study drug accountability throughout the study must be documented. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drugs to any persons except the subjects in this study.
- The investigator/pharmacist will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these study drugs.
- A study drug inventory will be maintained by the investigator/pharmacist. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the investigator/pharmacist agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and returned medication. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the person responsible.
- Used or unused study drug may be destroyed at the study center according to standard institutional procedures after drug accountability has been conducted by the sponsor or

representative, only if agreed upon by the sponsor. A copy of the standard institutional procedure for destroying investigational drugs will be provided to the sponsor or designee upon request. Unused study drug not destroyed at the site must be returned to the sponsor or designee at the end of the study or upon expiration.

4.4 Blinding

Not applicable. This is an open-label study.

4.5 Assignment and Allocation

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

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drugs and Other Medications

5.1.1 Dose/Dose Regimen and Administration Period

In this study, subjects will continue to receive 160 mg/day of MDV3100 until the investigator feels that continued use of MDV3100 is not beneficial to the subject, or the subject withdraws consent.

Since Astellas will close Study 9785-CL-0121, subjects that have not met any of the discontinuation criteria as outlined in Section 3.4 may be eligible to continue to receive treatment with enzalutamide in Study [redacted] upon approval and activation of this study at the participating institution.

Subjects who choose not to participate or are not eligible for Study [redacted] will complete their participation in Study 9785-CL-0121 by completing the safety follow-up visit upon activation of Study [redacted] at the institution.

Study drug should be taken as close to the same time each day as possible. Study drug can be taken with or without food. If dosing is missed on one day for any reason, double-dosing should not occur the following day.

5.1.2 Increase or Reduction in Dose of the Study Drugs

Subjects who experience a grade 3 or greater toxicity that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a grade 2 or lower severity. Subjects may subsequently be restarted on study drug at a reduced dose with the written approval of the sponsor. An increase in dose is not permitted.

5.1.3 Previous and Concomitant Medication (Drugs and Therapies)

All ongoing concomitant medications will be transcribed from the subject's previous MDV3100 study onto the appropriate eCRF for this study.

5.1.3.1 Previous Medication (Drugs and Therapies)

Not applicable as the subject is continuing from a prior MDV3100 study.

5.1.3.2 Concomitant Medication (Drugs and Therapies)

The following medications are prohibited while the subject is continuing on study drug:

- Concomitant medication that likely could cause clinical relevant drug-to-drug interactions with MDV3100
- Other (than MDV3100) AR antagonists (bicalutamide, flutamide, nilutamide)
- Investigational therapy other than MDV3100 or investigational procedures of any kind.

When applicable, the following medications should be maintained during the investigational period at the same dosage and schedule:

- LHRH agonist/antagonist.

Precautions Regarding Concomitant Medications

Please refer to the following links for an up-to-date list of CYP inhibitors, inducers, and substrates.

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency;
- http://medicine.iupui.edu/clinpharm/ddis/table.asp

Effects of MDV3100 on Exposure to Other Drugs

Clinical data indicate that MDV3100 is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Drugs with a narrow therapeutic index that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (e.g., phenytoin, warfarin), and CYP2C19 (e.g., S-mephenytoin) should be used with caution and may require dose adjustment as co-administration with MDV3100 may result in decreased exposure. If MDV3100 is co-administered with warfarin, conduct additional INR monitoring.

In consideration of the long half-life of MDV3100 (approximately 1 week), effects on enzymes may persist for 1 month or longer after stopping MDV3100.

Drugs That May Affect Exposure to MDV3100
Drugs that Inhibit or Induce CYP2C8

Co-administration of a strong CYP2C8 inhibitor (e.g., gemfibrozil) increased the composite AUC0-inf of MDV3100 plus its active metabolite in healthy volunteers; therefore, co-administration of MDV3100 with strong CYP2C8 inhibitors should be avoided, if possible.

The effects of CYP2C8 inducers on the PK of MDV3100 have not been evaluated in vivo. Co-administration of MDV3100 with strong or moderate CYP2C8 inducers (e.g., rifampin) may decrease the plasma exposure of MDV3100 and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP2C8 induction potential is recommended.

Drugs that Induce CYP3A4

The effects of CYP3A4 inducers on the PK of MDV3100 have not been evaluated in vivo. Co-administration of MDV3100 with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may decrease the plasma exposure of MDV3100 and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended. Moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) and St John's Wort may also reduce the plasma exposure of MDV3100 and should be avoided if possible.

5.1.4 Treatment Compliance

Study drug accountability will be performed to document compliance with the dosing regimen. Subjects will be asked to bring back all remaining study drug and all study drug packaging at each study visit for drug accountability.

5.1.5 Emergency Procedures and Management of Overdose

Neither the effects of overdose of MDV3100 nor an antidote to overdose are known. In case of overdose of MDV3100, symptomatic treatment with frequent monitoring is recommended.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Demographic information (date of birth, ethnicity, race as described by the subject and height) will be collected at screening of the prior study with MDV3100 and will be transcribed onto the appropriate eCRF for this study. Weight will be measured at every clinic visit including the safety follow-up visit.

5.2.2 Medical History

Medical history, to include any significant conditions or diseases other than prostate cancer that stopped at or prior to screening, will be recorded at screening of the prior study with MDV3100 and will be transcribed onto the appropriate eCRF for this study.

5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease

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

5.2.4 Performance Status

The ECOG scale [Oken et al, 1982] will be used to assess performance status.

Table 2 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

ECOG score will be collected at every clinic visit including the safety follow-up visit, see also the Schedule of Assessments (Section V, Table 1).

5.3 Pharmacokinetic Assessment

No PK assessment involved.

5.4 Safety Assessment

Please review the requirements related to the evaluation, reporting and analysis of Drug-Induced Liver Injury (DILI) information found in Appendix 2 (Liver Safety Monitoring and Assessment). In the event of a confirmed, marked hepatic abnormality as defined in Appendix 2 (Liver Safety Monitoring and Assessment), it is the investigator's responsibility to ensure contact with the sponsor/delegated CRO by telephone or fax immediately (i.e. within 24 hours of awareness).

5.4.1 Vital Signs

Vital signs including blood pressure, pulse rate, respiration rate, and temperature will be assessed prior to study drug administration, after the subject has rested for at least 5 minutes in the supine position, at every clinic visit while on study drug and at the safety follow-up visit (see also the Schedule of Assessments, Section V, Table 1).

5.4.2 Adverse Events

Adverse event collection will begin at the time of visit Day 1 and continue for 30 days after last dose of study drug. AEs will be documented at each clinic visit per the Schedule of Assessments. See Section 5.5 for details on AE collection.

Please refer to Appendix 2 (Liver Safety Monitoring and Assessment) for DILI adverse event assessment.

5.4.2.1 Adverse Events of Possible Hepatic Origin

Subjects with AEs of hepatic origin accompanied by Liver Function Test (LFT) abnormalities should be carefully monitored.

5.4.3 Laboratory Assessments

Please refer to Appendix 2 (Liver Safety Monitoring and Assessment) for additional DILI laboratory testing requirements and timing. Routine laboratory assessments for hematology and chemistry will be collected and analyzed at the local laboratory. Laboratory assessments will be assessed at every clinic visit including the safety follow-up visit, see also the Schedule of Assessments (Section V, Table 1). A maximum of 18 mL of blood will be taken at every visit. See also Appendix 1

If the results of clinical laboratory tests are outside the normal range and considered clinically significant, the investigator may decide to repeat tests on new samples.

Any changes in laboratory values will be evaluated by the investigator. Clinically important changes from the time of signing the informed consent will be reported as AEs.

5.4.3.1 Abnormal Liver Function Tests

If laboratory testing for a subject enrolled in a study and receiving study drug reveals an increase of serum aminotransferases (AT) to > 3x ULN, or bilirubin > 2x ULN, at least all four of the usual serum measures (ALT, AST, ALP, and total bilirubin [TBL]) should be repeated within 48 - 72 hours of notification of the test results. See Appendix 2 (Liver Safety Monitoring and Assessment) for additional information on monitoring and assessment of abnormal liver function tests.

Laboratory assessments must be obtained prior to study drug administration.

5.4.3.2 Hematology

Analytes to be tested include complete blood count (CBC), red blood cell count (RBC), hemoglobin (Hgb), hematocrit (HCT), white blood cell count (WBC), platelets, and WBC differential.

5.4.3.3 Chemistry

Analytes to be tested include sodium, potassium, calcium, chloride, magnesium, phosphate, glucose, creatinine, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total bilirubin, total protein, albumin, bicarbonate (CO_2), blood urea nitrogen (BUN).

5.4.4 Physical Examination

Standard, full physical examinations will be performed to assess weight, general appearance, skin, eyes, ears, nose, throat, neck, cardiovascular, chest and lungs, abdomen, musculoskeletal, neurologic status, mental status, lymphatic, genitourinary, and rectal

systems. Any abnormalities will be collected as medical history or AEs. Physical examination and weight will be recorded at every clinic visit including the safety follow-up visit, see also the Schedule of Assessments (Section V, Table 1).

5.4.5 Electrocardiogram (ECG)

The 12-lead ECG measurements will be performed at every time point according to the Schedule of Assessments after the subject has been in supine position for 5 minutes.

The investigator will review, sign and date the ECGs immediately after recording to ensure the subject's safety. The time and heart rate of the ECG, as well as an overall conclusion, will be recorded in the eCRF. This overall conclusion will be recorded as normal, abnormal not clinically significant, or abnormal clinically significant. If the overall conclusion is abnormal, the applicable abnormality code (provided in the eCRF) must be recorded in the eCRF.

Per time point, the ECG will be stored electronically, printed (photocopied to prevent fading of original print outs) and timely reviewed by the investigator. The original printout will be stored with the subject's source data. ECGs that have technical failures will not be stored.

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events (AEs)

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a study drug or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study drug
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

An AE observed after starting administration of the study drug is called a "treatment emergent adverse event" and usually summed up as the AEs in the clinical study report. If a diagnosis is made from the sign and/or symptom, the diagnosis should be recorded in preference to the listing of individual signs and symptoms. If not, the investigator should record each sign and symptom as an individual AE.

All AEs occurring after visit Day 1 should be recorded in the eCRF. All observed or spontaneously reported AEs will be recorded in the eCRF. Data to be recorded include a

description of the event, date and time of onset and end of the event, severity, action with respect to study drug, treatment required, relationship to study drug, and outcome of the event. All subjects who experience an AE will be followed up at appropriate time intervals until resolved or stabilized to the satisfaction of the investigator.

If an event recurs after it had resolved, it should be handled as a new AE. However, AEs that occur intermittently can be recorded as one AE. When the severity of an AE increases, the worst severity of that AE should be recorded for the entire duration.

5.5.2 Disease Progression

It is anticipated that a proportion of subjects will experience disease progression. Disease progression should not be reported as an AE. Clinical signs and symptoms due to disease progression will be collected as AEs. Individual signs and symptoms will be listed rather than the term “disease progression” with the following exception: if disease progression is the cause of death, this event may be recorded as an AE with “disease progression” as the reported term.

5.5.3 Definition of Serious Adverse Events (SAEs)

An adverse event is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death
- Is life threatening (an event is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Safety events of interest on a Sponsor medicinal product that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a Sponsor medicinal product
- Suspected abuse/misuse of a Sponsor medicinal product
- Inadvertent or accidental exposure to a Sponsor medicinal product
- Medication error involving a Sponsor product (with or without subject exposure to the Sponsor medicinal product, e.g., name confusion)

All of the events of interest noted above should be recorded on the eCRF. Any situation involving these events of interest that also meets the criteria for an SAE should be recorded on the AE page of the eCRF and marked 'serious' and the SAE worksheet.

The Sponsor has a list of events that they classify as 'always serious' events. If an adverse event is reported that is considered to be an event per this classification as 'always serious', additional information on the event may be requested.

5.5.4 Criteria for Causal Relationship to the Study Drug

Adverse events that fall under either "Possible" or "Probable" should be defined as "AEs whose relationship to the study drugs could not be ruled out". The following table describes the criteria for determining causal relationship of AEs.

Table 3 Criteria for Causal Relationship

Causal relationship to the study drug	Criteria for casual relationship
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration, which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re- administration (rechallenge) or withdrawal (dechallenge).

5.5.5 Criteria for Defining the Severity of an Adverse Event

Severity of AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0 of the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP). For terms not specified within NCI-CTCAE, the following guideline should be used to determine grade as below in Table 4

Table 4 Criteria for Severity of Adverse Event Terms Not Specified Within NCI-CTCAE

Grade	Description
1	Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self care activities of daily living
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

5.5.6 Reporting of Serious Adverse Events (SAEs)

In the case of a serious adverse event (SAE), the investigator must contact the Sponsor by telephone or fax immediately (within 24 hours of awareness). The investigator should complete and submit a report/report form containing all information that is required by the Regulatory Authorities to the Sponsor by fax immediately (within 24 hours of awareness). If the faxing of the report/report form or an SAE Worksheet is not possible or is not possible within 24 hours, the 24h contact for SAEs should be informed by phone. For contact details, see Section II Contact Details of Key Sponsor's Personnel.

Please email or fax the SAE Worksheet to:

Astellas Pharma Global Development,
Product Safety and Pharmacovigilance
Fax number: [redacted]
Email: [redacted]

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Director/Expert or his/her designee (see Section II Contact Details of Key Sponsor's Personnel).

Follow-up information for the event should be sent promptly (within 7 days) as necessary.

The sponsor or sponsor's designee will submit expedited safety reports (i.e. IND Safety Reports) to the regulatory agencies (i.e. FDA) as necessary, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their Institutional Review Board (IRB)/Independent Ethics Committee (IEC) within timelines set by regional regulations (i.e. EU, (e) CTD, FDA). Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site.

You may contact the sponsor's Medical Director/Expert for any other problem related to the safety, welfare, or rights of the study participant (subject/patient).

Full details of the SAE should also be recorded on the medical records and on the eCRF

The following minimum information is required:

- ISN/Study number
- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug.

SAEs will be collected from the time of study drug administration on Day 1 through 30 days after the last dose of study drug.

The Sponsor will notify all investigators responsible for ongoing clinical studies with the study drug of all SAEs which require submission to their IRB/IEC within timelines set by regional/country regulations.

The investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor.

For Suspected Unexpected Serious Adverse Reactions (SUSAR) from a blinded trial, unblinded CIOMS-I report will be submitted to the authorities and IRB/IEC where required.

All SAEs recorded up to 30 days after the last study drug intake should be reported, i.e. even if they occur after the end of study visit.

5.5.7 Follow-up to Adverse Events

All adverse events occurring during treatment are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized (all follow-up results are to be reported to the sponsor or delegated CRO).

For those subjects that transition to Study [redacted], it is not needed to collect AEs and SAEs after the last dose within this study, as these will be collected as part of the extension study.

For subjects who do not transition to Study [redacted], any adverse event that progresses to an "SAE" or if a subject experiences a new SAE, the investigator must immediately report the information to the sponsor.

Please refer to Appendix 2 (Liver Safety Monitoring and Assessment) for detailed instructions on DILI follow-up responsibilities related to history of symptoms, concomitant drug use, alcohol use, and recreational drug use.

5.5.8 Monitoring of Common Serious Adverse Events

Included in Appendix 3 (Common Serious Adverse Events) is a list of SAEs commonly anticipated to occur in the study population independent of drug exposure that will be monitored by the Sponsor throughout the course of the study for any change in frequency.

Any changes to this list will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events [Section 0].

5.5.9 Procedure in Case of Pregnancy

If during the conduct of the clinical trial, a male subject impregnates his partner, the subject should report the pregnancy to the investigator. The investigator should report the pregnancy to the sponsor as an SAE within 30 days from discontinuation of dosing. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated fertility date, pregnancy result and neonatal data etc., should be included in this information.

The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome to the sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)], the investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- ″Spontaneous abortion″ includes abortion and missed abortion.
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug.
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as ″possible″ by the investigator.
- In the case of a delivery of a living newborn, the ″normality″ of the infant is evaluated at the birth.
- ″Normality″ of the miscarried fetus is evaluated by visual examination unless test results which indicate a congenital anomaly are obtained prior to miscarriage.

5.5.10 Supply of New Information Affecting the Conduct of the Study

When new information becomes available, including "Dear Doctor Letters" but not limited to that, necessary for conducting the clinical study properly will lead to a protocol amendment, the sponsor should inform regulatory authorities, as well as all investigators involved in the clinical study, who will then inform the IRB/IEC of such information, and when needed, should amend the subject information.

5.6 Study Drug Concentration

None.

5.7 Other Measurements, Assessments, or Methods

None.

5.8 Total Amount of Blood

The total amount of blood for each subject will vary depending on how long they stay on treatment. The maximum amount of blood collected at each clinic visit is approximately 18 ml.

Furthermore, if any laboratory abnormalities are found for a subject, additional blood may be drawn for monitoring.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation is a subject who enrolled in the study and for whom study treatment is permanently discontinued prematurely for any reason.

A safety follow-up visit will be performed approximately 30 days after the last dose of study drug, or prior to the initiation of another anti-neoplastic therapy, whichever occurs first.

For subjects who enroll into Study [redacted], a safety follow-up visit is not required. For these subjects, the final visit for Study 9785-CL-0121 will serve as Day 1 for Study [redacted] (±7 days).

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

Subjects who choose not to participate or are not eligible for Study [redacted] will complete their participation in Study 9785-CL-0121 by completing the safety follow-up visit upon activation of Study [redacted] at the institution.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor of the discontinuation and the reason for it.

6.3 Discontinuation of the Study

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

This is a phase 2, open-label, extension study for subjects who are benefiting from administration of MDV3100 in a prior named study. No formal statistical analyses will be conducted. Descriptive summary statistics will be produced for all parameters.

7.1 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.

7.2 Analysis Set

7.2.1 Safety Analysis Set (SAF)

The SAF is defined as all subjects who have taken at least one dose of study drug in this extension study.

7.3 Demographics and Other Baseline Characteristics

Descriptive summary statistics will be produced for all parameters.

7.4 Analysis of Efficacy

Not applicable.

7.5 Analysis of Safety

Descriptive summary statistics will be produced for all parameters. Safety analyses will be conducted using the SAF.

7.5.1 Adverse Events

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 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.

AEs will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Authorities (MedDRA) and graded using NCI-CTCAE. Listings of deaths, SAEs, and withdrawals due to AEs 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. 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.

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.

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.

7.5.6 Concomitant Medications

The frequency of concomitant medications (prescription, over-the-counter, and nutritional supplements) will be summarized by preferred term. Medications will be coded using the World Health Organization (WHO) drug dictionary. 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.

7.5.7 Extent of Exposure

Duration of treatment and total dose administered will be summarized.

7.6 Analysis of Pharmacokinetics

None.

7.7 Protocol Deviations and Other Analysis

Protocol deviations as defined in Section 8.1.6 will be summarized for all subjects and by site. 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

Descriptive summary statistics will be produced for ECOG.

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

An interim analysis will be performed when deemed to be necessary (e.g. as part of a submission).

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

7.9.1 Missing Data

Imputations for missing data, if applicable, will be addressed in the statistical analyses plan.

7.9.2 Visit Windows

Visit windows are allowed for certain visits per the schedule of procedures. Subject data will not be excluded from analyses due to the subject's failure to comply with the visit schedule.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The investigator or designee will enter data collected using an Electronic Data Capture (EDC) system.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Laboratory tests are performed at the local laboratory.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included (but is not limited to) in the source medical records:

- Demographic data (age, sex, race, ethnicity, weight and height)
- Records to support inclusion and exclusion criteria details

- Participation in study and signed and dated informed consent form
- Visit dates
- Disease and prior treatment history. Photocopies or fax documents of original records are acceptable if obtained from an outside institution
- Medical history
- Physical examination details
- Key safety data as specified in the protocol
- Adverse events and concomitant medication
- Results of protocol specified evaluations (laboratory, ECG)
- Dispensing, destruction, and return of study drug details
- Reason for discontinuation
- Subject number
- Staff notes and phone records
- Medical records from other departments or hospitals, including discharge summaries, correspondence, etc., at which the subject received treatment. Photocopies or fax documents of original records are acceptable if obtained from an outside institution.

8.1.3 Clinical Study Monitoring

The sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents (refer to Section 8.1.2 "Specification of Source Documents") when they are requested by the sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data management will be overseen by the responsible department at the sponsor in accordance with the standard operating procedures for data management. All study specific processes and definitions will be documented by Data Management. eCRF retrieval and correction process will be referenced in the eCRF instructions. Coding of medical terms will be performed using MedDRA.

The study database will be soft-locked when all data that are specified in the study protocol to be collected have been received and cleaned according to applicable SOPs. It will be hard-locked when a data review meeting has been held, and all data related decisions have been made and reflected in the database.

8.1.6 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systemic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purpose of this protocol, deviations requiring notification to Sponsor are defined as any subject who:

- Entered into the study even though they did not satisfy entry criteria
- Developed withdrawal criteria during the study and not withdrawn
- Received wrong treatment or incorrect dose
- Received excluded concomitant treatment

When a deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the Sponsor is notified. The Sponsor will follow-up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study. If a deviation impacts the safety of a subject the investigator must contact the Sponsor immediately.

The investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the Sponsor and maintained within the Trial Master File (TMF).

NOTE: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

8.1.7 End of Trial

The end of trial in all participating countries is defined as the Last Patient's Visit.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB)/ Independent Ethics Committee(IEC)/ Competent Authorities (CA)

The clinical study may begin after acquisition of a written approval from the Institutional Review Board/Independent Ethics Committee/ Competent Authorities of record for that site and study.

The protocol and the required supporting documents will be submitted to the CA according to the national laws. Prior to starting the study, approval must be obtained in writing, where applicable.

The investigator shall make accurate and adequate written progress reports to the IRB/IEC at appropriate intervals, not exceeding one year. The investigator shall make an accurate and adequate final report to the IRB/IEC within 90 days after the close-out visit.

8.2.2 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to GCP, ICH Guidelines and the applicable laws and regulations.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

Prior to execution of the clinical study, the investigator should prepare the written informed consent form and other written information in collaboration with the sponsor and revise the information whenever necessary. The written informed consent form and any other written information should be submitted to the sponsor and be subject to prior approval by the IRB/IEC.

- The investigator/sub-investigator is responsible for explaining the nature and purpose of the study as well as other study-related matters to subjects, using the written information, and for obtaining their full understanding and written consent to participate in the study of their own free will.
- The investigator or other responsible personnel who provided explanations (including collaborators who gave supportive information, if applicable) and the subject should sign and date the written information, or write down his/her name, and date the form.
- Informed consent must be obtained by the time that the first observations / examinations of the pre-investigational period are performed. Guardian consent should be obtained from the proxy consenter, before start of pre-investigational period.
- The investigator or other responsible personnel must give a copy of the signed consent form to the subject and store the original appropriately in accordance with the rules at the study site concerned.
- The investigator or other responsible personnel should note the following when obtaining consent from subjects:

- No subject may be subjected to undue influence, such as compulsory enrollment into a study.
- The language and expressions used in the written information should be as plain and understandable as possible. Subjects should be given the opportunity to ask questions and receive satisfactory answers to the inquiry, and should have adequate time to decide whether or not to participate in the study. Written information should not contain any language or contents that causes the subject to waive or appears to waive any legal rights, or that releases/mitigates or appears to release/mitigate the study site, the investigator/sub-investigator, collaborators, or the sponsor from liability for negligence.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

1. The investigator/sub-investigator will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study (e.g., report of serious adverse drug reactions). The communication should be documented in the subject's medical records, and it should be confirmed whether the subject is willing to remain in the study or not.
2. If the investigator recognizes the necessity to revise the written information in the terms and conditions applicable to paragraph 1, the written information should be revised immediately based upon the newly available information, and be re-approved by the IRB/IEC.
3. The investigator/sub-investigator should obtain written informed consent to continue participation with the revised written information defined in paragraph 2, even if subjects are already informed of the relevant information orally. The investigator or other responsible personnel who provided explanations (including collaborators who gave supportive information, if applicable) and the subject should sign and date the informed consent form, or write down his/her name and date the form. The investigator or other responsible personnel should give a copy of the signed informed consent form to the subject who had given consent with the written information and store the original appropriately as done for the previous informed consent.

8.2.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The sponsor, its board members and its personnel shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

The sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by the sponsor. However, the sponsor requires the investigator to permit the sponsor, sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The sponsor will ensure that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e., HIPAA).

If applicable, for US sites, the HIPAA Privacy Rule provides federal protection for the privacy of PHI by implementing standards to protect and guard against the misuse of individually identifiable health information of subjects participating in sponsored clinical trials. "Authorization" is required from each research subject, i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual's PHI. A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization may be combined into the Informed Consent document (approved by the IRB/IEC) or it may be a separate document (approved by the IRB/IEC or designed PB) or provided by the investigator or sponsor (without IRB/IEC or Privacy Board [PB] approval). It is the responsibility of the investigator and institution to obtain such waiver/authorization in writing from the appropriate individual.

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

The study will be considered for publication or presentation at (scientific) symposia and congresses. The investigator will be entitled to publish or disclose the data generated at their respective study site only after allowing the sponsor to review all transcripts, texts of presentations, and abstracts related to the study at least 90 days prior to the intended submission for publication or any other disclosure for Astellas Pharma sponsored studies. This

is necessary to prevent premature disclosure of trade secrets or patent-protected information and is in no way intended to restrict publication of facts or opinions formulated by the investigator. The sponsor will inform the investigator in writing of any objection or question arising within 30 days of receipt of the proposed publication material.

8.3.2 Documents and Records Related to the Clinical Study

The sponsor will provide the investigator and/or institution with the following:

- Study protocol (and amendments, as applicable)
- Investigator's Brochure (and amendments, as applicable)
- eCRFs and SAE Report Form
- Investigator's File
- Study drug with all necessary documentation
- Study contract
- Approval of regulatory authority and all documents related to submission
- Investigational Medicinal Product Dossier (IMPD) (if applicable per local regulations)

In order to start the study, the investigator and/or study site is required to provide the following documentation to the sponsor:

- Financial disclosure in compliance with federal regulation 21CFR Part 54
- Submission letter to IRB/IEC
- Signed confidentiality agreement
- Signed Investigator's Statement in this protocol
- Executed Study Contract
- Signed and dated FDA form 1572, if applicable
- Copy of the approved ICF and separate authorization form, if appropriate.
- IEC/IRB approval of the protocol, protocol amendments (if applicable) and ICF (and separate authorization form, if appropriate), stating clearly the sponsor's name, study number and study drug, including a membership list with names and qualifications.
- Current Curricula Vitae of all investigators (signed and dated, brief and in English)
- Laboratory normal reference ranges (if applicable, signed and dated by the responsible laboratory employee)
- Medical/Laboratory/Technical procedures/tests certifications or accreditations or established quality control or other validation, where required.

At the end of the study, the sponsor is responsible for the collection of:

- Study documentation, forms etc.
- Unused study drug

The investigator will archive all study data (e.g., Subject Identification Code List, source data, eCRFs, and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation. It is recommended, however, that records be retained for at least five years in the event follow-up is necessary to help determine any potential hazards to subjects who took part in the study. The sponsor will notify

the investigator if the Marketing Authorization Application (MAA) is approved or if the IMPD is discontinued. The investigator agrees to obtain the sponsor's agreement prior to disposal, moving, or transferring of any study-related records.

The sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. All data will be entered on eCRFs supplied for each subject.

The investigator and sponsor will mutually agree upon the storage format for the retention of electronic data.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or administrative changes/non-substantial amendments. Depending on the nature of the amendment and/or administrative change, either IRB/IEC approval or notification is required. The changes will become effective only after the approval of the sponsor, the investigator, the regulatory authority, and the IRB/IEC (if applicable).

Amendments to this protocol must be signed by the sponsor and the investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local/national regulation.

8.3.4 Insurance of Subjects and Others

The sponsor, Astellas Pharma Europe B.V., has covered this study by means of an insurance of the study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's File.

8.3.5 Investigator Indemnity

The sponsor agrees to, and does hereby, indemnify, defend and hold the investigator harmless from and against all claims, demands, actions, and proceedings which may be brought or asserted against the investigator to recover damages and losses for or attributable to bodily injury, sickness, disease, or death arising from or alleged to arise from or be reasonably attributable to this study.

Notwithstanding the foregoing, the sponsor does not, however, agree to indemnify, defend or hold the investigator harmless from claims, demands, actions, proceedings or damages resulting or claimed to have resulted from:

- Failure of the investigator to evaluate or properly interpret available information that is relevant to this study, and for independent decisions made as the result of such failure;
- Failure of the investigator to adhere to all provisions of the protocol for this study and to written recommendations and written instructions delivered to the investigator by the sponsor concerning the administration and use of drug substances, including the placebo, involved in this study;
- Failure of the investigator to render professional service or to conduct this study in a normal, prudent manner.

A condition of this indemnity obligation is that, whenever the investigator has information from which it may be reasonably concluded that an incident of bodily injury, sickness, disease or death has occurred, the investigator shall immediately give notice to the sponsor of all pertinent data surrounding any such incident, and, in the event a claim is made or a suit is brought, the investigator shall assist the sponsor and cooperate in the gathering of information with respect to the time, place, and circumstances and in obtaining the names and addresses of the injured parties and available witnesses. The investigator shall not, except at his own cost, voluntarily make any payment or incur any expense in connection with any such claim or suit without the prior written consent of the sponsor.

8.3.6 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the Coordinating Investigator(s) or the Principal Investigator(s). The representative for the Coordinating Investigator(s) or the Principal Investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for Coordinating Investigator(s) or the Principal Investigator(s) will be selected from the participating investigators by the Sponsor prior to database lock.

9 QUALITY ASSURANCE

The sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (record), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The sponsor or sponsor's designee may arrange to inspect/audit the clinical study at any or all investigational sites. The auditor is independent from the clinical monitoring and project management team at the sponsor. The audit may include on-site review of regulatory documents, case report forms, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Data Monitoring Committee

Not applicable.

10.2 Other Evaluation Committee(s)

Not applicable.

10.3 Other Study Organization

Not applicable.

11 REFERENCES

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Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, Redfern CH, Ferrari AC, Dreicer R, Sims RB, Xu Y, Frohlich MW, Schellhammer PF. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363: 411-422.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. 1982;6:649-655.

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Scher HI, Buchanan G, Gerald W, Butler LM, Tilley WD. Targeting the androgen receptor: improving outcomes for castration-resistant prostate cancer. Endocr Relat Cancer 2004; 11(3):459-476.

Tannock IF, de WR, Berry WR et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; 351(15):1502-1512.

Tran C, Ouk S, Clegg NJ et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009; 324(5928): 787-790.

http://medicine.iupui.edu/clinpharm/ddis/table.asp

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency

Company Reports

Protocol 9785-CL-0007. Current version

Protocol 9785-CL-0003. Current version

Investigator's Brochure. MDV3100 for the treatment of cancer. Current edition.

12 APPENDICES

12.1 Appendix 1: Laboratory Tests

Test type	Visit	Parameters to be analyzed
Hematology	All visits	Hemoglobin (Hgb) Hematocrit (HCT) Complete Cell Count (CBC) Red Blood Cells (RBC) White blood cells (WBC) Differential WBC Platelets
Biochemistry	All visits	sodium potassium calcium chloride magnesium phosphate glucose creatinine alkaline phosphatase alanine aminotransferase (ALT) aspartate aminotransferase (AST) gamma-glutamyl transferase (GGT) total bilirubin total protein albumin bicarbonate (CO_2) blood urea nitrogen (BUN)

12.2 Appendix 2: Liver Safety Monitoring and Assessment

If laboratory testing for a subject enrolled in study and receiving study drug reveals an increase of serum aminotransferases (AT) to > 3X ULN, or bilirubin > 2X ULN, at least all four of the usual serum hepatic measures (ALT, AST, ALP, and bilirubin [TBL])) should be repeated. Testing should be repeated within 48-72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central lab regarding moderate and marked liver abnormality to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and marked where ULN:

	ALT or AST		**Total Bilirubin**
Moderate	> 3 x ULN	or	> 2 x ULN
Marked	> 3 x ULN	and	> 2 x ULN

In addition, the subject should be considered to have marked hepatic abnormalities for any of the following:

- ALT or AST > 8X ULN
- ALT or AST > 5X ULN for more than 2 weeks
- ALT or AST > 3X ULN and INR > 1.5
- ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or marked abnormalities and require additional monitoring and follow-up. Discontinuation of treatment must occur if subject has marked abnormalities. In addition, if closed monitoring for a subject with moderate hepatic laboratory tests is not possible, drug should be discontinued.

Follow-up Procedures

Confirmed moderate and marked abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site should complete the Liver Abnormality Case Report Form (LA-CRF) or an appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal liver function tests (LFTs) should be repeated 2-3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

Marked hepatic liver function abnormalities, in the absence of another etiology, may be considered an important medical event and reported as a Serious Adverse Event (SAE). The

sponsor should be contacted and informed of all subjects for whom marked hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset-diseases should be recorded as 'adverse events' on the AE page of eCRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis (NASH) is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels. The investigator should ensure that the medical history form captures any illness that pre-dates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including non-prescription medication, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, including dose, should be entered on the concomitant medication page of eCRF. Information on alcohol, other substance use, and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents
- Based on the subject's history, other testing may be appropriate including:
    - acute viral hepatitis (A,B, C, D, E or other infectious agents)
    - ultrasound or other imaging to assess biliary tract disease
    - other laboratory tests including INR, direct bilirubin.
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Discontinuation

In the absence of an explanation for increased LFTs, such as viral hepatitis, pre-existing or acute liver disease or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The investigator may determine that it is not in the subject's best interest to continue study enrollment.

Discontinuation of treatment must occur if:

- ALT or AST > 8X ULN
- ALT or AST > 5X ULN for more than 2 weeks
- ALT or AST > 3X ULN and (TBL > 2X ULN or INR > 1.5)

Discontinuation of treatment should be considered if:

- ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

In addition, if close monitoring for a subject with moderate or marked hepatic laboratory tests is not possible, drug should be discontinued.

Reference

Guidance for Industry titled “Drug-Induced Liver Injury: Premarketing Clinical Evaluation” issued by FDA on July 2009.

12.3 Appendix 3: Common Serious Adverse Events

The following list of serious adverse events are considered common for the study population defined in this protocol and should be reported by the investigator as described in Section 0. For IND safety reporting, single occurrences of the following events may be excluded from expedited reporting. If aggregate analysis of these events indicates they occur more frequently with study drug, an expedited IND safety report may be submitted to FDA.

- Anemia
- Anorexia
- Asthenia / Fatigue
- Back pain
- Bone pain
- Catheter related infection
- Dyspnea
- Haematuria
- Hydronephrosis
- Metastases to bone
- Metastases to central nervous system
- Nausea
- Obstructive uropathy
- Pain
- Prostate cancer metastatic
- Renal failure
- Renal failure acute
- Spinal compression fracture
- Spinal cord compression
- Urinary retention
- Urinary tract infection
- Urinary tract obstruction
- Vomiting

13 ATTACHMENT 1: SUBSTANTIAL AMENDMENT 4

I. The purpose of this amendment is:

Substantial Changes
1. Revise Study Design
DESCRIPTION OF CHANGE:
Subjects who are continuing to derive clinical benefit from treatment with enzalutamide based on the investigator's medical opinion and have not met any of the discontinuation criteria as outlined in Section 3.4 of the protocol may be eligible to continue to receive treatment with enzalutamide in Study [redacted] upon approval of the protocol and activation of this study at the participating institution. Subjects who choose not to participate or are not eligible for Study [redacted] will complete their participation in Study 9785-CL-0121 by completing the safety follow-up visit upon activation of Study [redacted] at the institution.
RATIONALE:
Astellas will close Study 9785-CL-0121 and allow subjects who are continuing to derive clinical benefit from treatment with enzalutamide to enroll in Study [redacted]. Study [redacted] allows investigators to follow their subjects per standard of care while still providing treatment with enzalutamide for their prostate cancer.

Nonsubstantial Changes
1. Update Sponsor contact information
DESCRIPTION OF CHANGE:
Change of Astellas Medical Expert/Medical Monitor.
RATIONALE:
Key sponsor personnel change.
2. Revise planned study period
DESCRIPTION OF CHANGE:
Change planned study period to indicate an end date of first quarter 2017.
RATIONALE:
The planned study period is updated to reflect the most current information.

II. Amendment Summary of Changes:

IV Synopsis, Design and Methodology and 2 Study Objective(s), Design and Endpoints *2.2.1 Study Design*
WAS:
This is a multi-center phase 2 open-label extension study in subjects with prostate cancer who have completed MDV3100 treatment in a previous study with MDV3100 to assess the long-term safety of continued administration of MDV3100, when judged by the investigator to be in the best interest of the subject. For the study duration, all subjects with castration-resistant prostate cancer (CRPC) will have to maintain androgen deprivation with an LHRH agonist/antagonist unless they underwent bilateral orchiectomy. 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 assessment. Throughout the study, safety and tolerability will be assessed by the recording of adverse events, 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.
IS AMENDED TO:
This is a multi-center phase 2 open-label extension study in subjects with prostate cancer who have completed MDV3100 treatment in a previous study with MDV3100 to assess the long-term safety of continued administration of MDV3100, when judged by the investigator to be in the best interest of the subject. For the study duration, all subjects with castration-resistant prostate cancer (CRPC) will have to maintain androgen deprivation with an LHRH agonist/antagonist unless they underwent bilateral orchiectomy. 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 assessment. Throughout the study, safety and tolerability will be assessed by the recording of adverse events, 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 from their last dose of study drug.~~ **Subjects that have not met any of the discontinuation criteria as outlined in Section 3.4 may be eligible to continue to receive treatment with enzalutamide in Study [redacted] upon approval and activation of this study at the participating institution. Subjects who enroll in Study [redacted] will not be required to have a safety follow- up visit.** **Subjects who choose not to participate or are not eligible for Study [redacted] will complete their participation in Study 9785-CL-0121 by completing the safety follow-up visit upon activation of Study [redacted] at the institution.**

IV Synopsis, Discontinuation Criteria

ADDED:

Astellas will be closing Study 9785-CL-0121. Subjects that have not met any of the discontinuation criteria as outlined in Section 3.4 may be eligible to continue to receive treatment with enzalutamide in Study [redacted] upon approval and activation of this study at the participating institution.

Subjects who choose not to participate or are not eligible for Study [redacted] will complete their participation in Study 9785-CL-0121 by completing the safety follow-up visit upon activation of Study [redacted] at the institution.

V Schedule of Assessments

Table 1: Schedule of Assessments

WAS:

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	

g. 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.

h. 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.

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

IS AMENDED TO:

Study Day	-32 to -1	1[a]	29	85	every 12 weeks up to week 85	every **24**[d] weeks from week 85	Safety FU[e, f]
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) If the subject is eligible to continue in extension Study [redacted], the final visit of Study 9785-CL-0121 will serve as the initial visit (day 1) for extension Study [redacted]. Subjects who enroll in Study [redacted] will not be required to have a safety follow-up visit.

e) If a new cytotoxic or investigational anticancer treatment is initiated before 30 days after last dose, then safety follow-up for Study 9785-CL-0121 should occur immediately before starting the new treatment.

f) Subjects who choose not to participate or are not eligible for Study [redacted] will complete their participation in Study 9785-CL-0121 by completing the safety follow-up visit upon activation of Study [redacted] at the institution.

3 Study Population

3.4 Discontinuation Criteria for Individual Subjects

WAS:

Unless the subject withdraws consent, all subjects discontinuing study drug for any reason will have a safety follow-up visit 30 days after their last dose of MDV3100.

IS AMENDED TO:

Unless the subject withdraws consent, all subjects discontinuing study drug for any reason will have a safety follow-up visit 30 days after their last dose of MDV3100. **For subjects who enroll into Study [redacted], a safety follow-up visit is not required. For these subjects the final visit for Study 9785-CL-0121 will serve as Day 1 for Study [redacted] (±7 days).**

5 Treatments and Evaluation

5.1.1 Dose/Dose Regimen and Administration Period

WAS:

In this study, subjects will continue to receive 160 mg/day of MDV3100 until the investigator feels that continued use of MDV3100 is not beneficial to the subject, or the subject withdraws consent.

Study drug should be taken as close to the same time each day as possible. Study drug can be taken with or without food. If dosing is missed on one day for any reason, double-dosing should not occur the following day.

IS AMENDED TO:

In this study, subjects will continue to receive 160 mg/day of MDV3100 until the investigator feels that continued use of MDV3100 is not beneficial to the subject, or the subject withdraws consent.

Since Astellas will close Study 9785-CL-0121, subjects that have not meet any of the discontinuation criteria as outlined in Section 3.4 may be eligible to continue receive treatment with enzalutamide in Study [redacted] upon approval and activation of this study at the participating institution.

Subjects who choose not to participate or are not eligible for Study [redacted] will complete their participation in Study 9785-CL-0121 by completing the safety follow-up visit upon activation of Study [redacted] at the institution.

Study drug should be taken as close to the same time each day as possible. Study drug can be taken with or without food. If dosing is missed on one day for any reason, double-dosing should not occur the following day.

5 Treatments and Evaluation

5.5.7 Follow-up of Adverse Events

WAS:

All adverse events occurring during the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized (all follow-up results are to be reported to the sponsor or delegated CRO).

Since it is unpredictable how long such a follow-up will take, data from this follow-up generated after the subject's end of the study visit will be recorded by the investigator. Full details regarding this follow-up will be described in the study report, whenever necessary.

If during adverse event follow-up, the adverse event progresses to an "SAE" or if a subject experiences a new SAE, the investigator must immediately report the information to the sponsor.

Please refer to Appendix 2 (Liver Safety Monitoring and Assessment) for detailed instructions on DILI follow-up responsibilities related to history of symptoms, concomitant drug use, alcohol use, and recreational drug use.

IS AMENDED TO:

All adverse events occurring during ~~the study~~ **treatment** are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized (all follow-up results are to be reported to the sponsor or delegated CRO).

~~Since it is unpredictable how long such a follow-up will take, data from this follow-up generated after the subject's end of the study visit will be recorded by the investigator. Full details regarding this follow-up will be described in the study report, whenever necessary.~~

For those subjects that transition to Study [redacted], it is not needed to collect new AEs and SAEs after the last dose within this study, as these will be collected as part of the extension study.

~~If during adverse event follow-up, the~~ **For subjects who do not transition to Study [redacted] any** adverse event **that** progresses to an "SAE" or if a subject experiences a new SAE, the investigator must immediately report the information to the sponsor.

Please refer to Appendix 2 (Liver Safety Monitoring and Assessment) for detailed instructions on DILI follow-up responsibilities related to history of symptoms, concomitant drug use, alcohol use, and recreational drug use.

6 Discontinuation

6.1 Discontinuation of Individual Subject(s)

WAS:

A discontinuation is a subject who enrolled in the study and for whom study treatment is permanently discontinued prematurely for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

IS AMENDED TO:

A discontinuation is a subject who enrolled in the study and for whom study treatment is terminated discontinued prematurely for any reason.

A safety follow-up visit will be performed approximately 30 days after the last dose of study drug, or prior to the initiation of another anti-neoplastic therapy, whichever occurs first.

For subjects who enroll into Study [redacted], a safety follow-up visit is not required. For these subjects, the final visit for Study 9785-CL-0121 will serve as Day 1 for Study [redacted] (±7 days).

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

Subjects who choose not to participate or are not eligible for Study [redacted] will complete their participation in Study 9785-CL-0121 by completing the safety follow-up visit upon activation of Study [redacted] at the institution.

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IV Synopsis, Planned Study Period
WAS:
From 3Q2011 onwards
IS AMENDED TO:
From 3Q2011 ~~onwards~~ **to 1Q2017**

14 SPONSOR'S SIGNATURES

ELECTRONIC SIGNATURE PAGE

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