Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: To be determined		
Name of Active Ingredient: MDV3100		

SYNOPSIS

Title of Study: A Phase 1-2, Open-Label, Uncontrolled, Dose-Escalation Study of MDV3100 in Patients with Castration-Resistant Prostate Cancer (Protocol No. 9785-CL-0111)

Investigators/Coordinating Investigator: [redacted], MD, etc.

Study Center(s): The study was conducted at 27 sites in Japan.

Publication Based on the Study: None

Study Period:

Study Initiation Date (Date of First Informed Consent): 2 November 2010

Study Completion Date (Date of Last Evaluation): 2 July 2014

Phase of Development: Phase 1-2

Objectives:

Dose-Escalation Cohort: To determine the safety, tolerability and pharmacokinetics (PK) of MDV3100 when administered orally to patients with castration-resistant prostate cancer (CRPC patients).

Expansion Cohort: To determine the efficacy, safety and PK of MDV3100 when administered orally to patients with CRPC who have previously been treated with chemotherapy including docetaxel (post-chemo CRPC patients).

Methodology: This study was an open-label, uncontrolled study conducted in Japan, involving a Dose-Escalation Cohort and an Expansion Cohort. In the Dose-Escalation Cohort, the oral dose of MDV3100 was escalated to the next dose while evaluating the safety, tolerability and PK in CRPC patients. In the Expansion Cohort, the efficacy and safety of MDV3100 at the recommended dose determined in non-Japanese subjects were evaluated in post-chemo CRPC patients.

The starting dose level was 80 mg in the Dose-Escalation Cohort and 3 patients were enrolled in this 80-mg group. Similarly, 3 patients were enrolled in the subsequent 160-mg and 240-mg groups. After the tolerability and preliminary PK of MDV3100 at 160 mg were evaluated in the Dose-Escalation Cohort, evaluation of the efficacy, safety and PK at a dose of 160 mg was begun in the Expansion Cohort.

The Dose-Escalation Cohort consisted of 5 periods: Screening Period, Single-Dose Period, Multiple-Dose Period, Long-Term Dosing Period and Safety Follow-Up Period. The Expansion Cohort consisted of 4 periods: Screening Period, Multiple-Dose Period, Long-Term Dosing Period, and Safety Follow-Up Period. The subjects in the Long-Term Dosing Period remained on study treatment until one of the discontinuation criteria was met (up to marketing approval).

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Name of Finished Product: To be determined		
Name of Active Ingredient: MDV3100		

Number of Patients (Planned, Enrolled and Analyzed):

Planned

Dose-Escalation Cohort: 9 patients (3 patients each in the 80-, 160- and 240-mg groups)

Expansion Cohort: 37 patients

Analyzed

Dose-Escalation Cohort:

- Safety analysis set (SAF): 9 patients
- Full analysis set (FAS): 9 patients
- Per protocol set (PPS): 2 patients
- Pharmacokinetic analysis set (PKAS): 9 patients

Expansion Cohort:

- SAF: 38 patients
- FAS: 38 patients
- PPS: 38 patients
- PKAS: 38 patients

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

At provisional registration, a patient who met the following inclusion criteria was eligible:

1. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features;
2. Ongoing androgen deprivation therapy with a GnRH analogue or a bilateral orchiectomy;
3. No history of a bilateral orchiectomy, but with a plan to maintain effective GnRH analogue therapy for the duration of the trial;
4. For a patient receiving zoledronate therapy, no change of a dose for at least 4 weeks prior to study drug treatment;
5. Progressive disease (PD) after anti-androgen therapy (medical or surgical castration). Disease progression was defined by one or more of the following 3 criteria:
   - Progression as defined by Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1);
   - Progression as defined by three consecutive rising prostate-specific antigen (PSA) levels with an interval of ≥1 week between each determination;
   - Progression as defined by two or more new lesions on a bone scan.
6. History of no more than two prior chemotherapy regimens with at least one regimen containing docetaxel, if present;

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Name of Finished Product: To be determined		
Name of Active Ingredient: MDV3100		

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (2 was allowed only if due to bone pain);
8. Confirmation of documented metastatic disease by diagnostic imaging;
9. Aged ≥20 years at the time of providing written informed consent;
10. Written informed consent had been obtained;
11. Consent had been obtained for adherence to an appropriate barrier method (condom or pessary) for the prevention of pregnancy from the start of the study until 3 months after the last dose of study drug.

For the Expansion Cohort, a patient who met the following inclusion criteria in addition to the above criteria was eligible:

12. Presence of measurable metastatic lesions as determined by the RECIST;
13. History of no more than two prior chemotherapy regimens with at least one regimen containing docetaxel.

At final registration, a patient who met criterion 3 and the following inclusion criteria was eligible:

14. Serum testosterone level <0.50 ng/mL at screening;
15. Serum PSA level ≥2 ng/mL at screening.

Exclusion Criteria

At provisional registration, a patient who met any of the following exclusion criteria was excluded:

1. Metastases in the brain or active epidural disease (Note: a patient with treated epidural disease was eligible);
2. History of a malignancy other than adenocarcinoma of the prostate within the previous 5 years;
3. Use of bicalutamide within 6 weeks prior to study drug treatment; or use of an androgen receptor signalling inhibitor other than bicalutamide, 5-α reductase inhibitors (finasteride, dutasteride) within 4 weeks prior to study drug treatment;
4. Use of estrogens within 3 weeks prior to study drug treatment;
5. Use of supplements or herbal products that may decrease PSA levels (i.e., saw palmetto) within 4 weeks prior to study drug treatment;
6. Use of steroids at doses greater than the equivalent of 10 mg of prednisolone per day within 4 weeks prior to study drug treatment;
7. Previous participation in a clinical study of androgen synthesis inhibitor/androgen receptor inhibitor; or participation in another clinical study within 4 weeks prior to study drug treatment;
8. Radiation therapy within 12 weeks prior to study drug treatment;
9. Any condition that, in the opinion of the investigator, would impair the patient's ability to comply with study procedures;
10. Evidence of severe or uncontrolled systemic disease other than CRPC;
11. Evidence of serious drug hypersensitivity;

Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: To be determined		
Name of Active Ingredient: MDV3100		

12. History of seizure, including any febrile seizure, loss of consciousness, or transient ischemic attack within 12 months prior to study drug treatment, or any condition that may pre-dispose to seizure (e.g., prior stroke, brain arteriovenous malformation, head trauma with loss of consciousness requiring hospitalization);
13. Use of the following medications known to lower the seizure threshold or prolong the QT interval within 28 days prior to study drug treatment (shown specifically in Appendix 1 of the protocol [Appendix 13.1.1]):

—Medications known to lower the seizure threshold,

- Aminophylline/theophylline;
- Atypical antipsychotics;
- Insulin;
- Lithium;
- Pethidine;
- Phenothiazine antipsychotics;
- Tricyclic and tetracyclic antidepressants.

—Medications known to prolong the QT interval,

- Class Ia and III antiarrhythmics;
- Droperidol;
- Moxifloxacin;
- Macrolide antibiotics;
- Pimozide.

14. Chemotherapy infusion within 4 weeks prior to screening.

At final registration, a patient who met any of criteria 1, and 9 to 11 at the provisional registration or any of the following exclusion criteria was excluded:

15. Granulocyte count <1500/μL or platelet count <10 × 10^4/μL or hemoglobin (Hb) <9 g/dL at screening (Note: patient treated with a growth factor or blood transfusion within 7 days prior to screening were not allowed);
16. Total-bilirubin (T-bil), ALT (alanine aminotransferase) or AST(aspartate aminotransferase) >2 × the upper limit of normal at screening;
17. Serum creatinine (Cr) >2 mg/dL at screening.

Product, Dose and Mode of Administration, Batch Numbers: MDV3100 soft gelatin capsule 40 mg (Lot No. [redacted], [redacted])

The subjects received the study drug orally at a dose of 80 mg, 160 mg, or 240 mg once daily after breakfast. The investigator or sub-investigator instructed the subjects to take the study drug as close as possible to the same time each day. On visit days when blood sampling for PK evaluation was scheduled, the dose time was adjusted.

Treatment in each period was as follows:

Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: To be determined		
Name of Active Ingredient: MDV3100		

1. Single-Dose Period

On Day S1 (Visit 1-1), subjects in the 80-mg, 160-mg and 240-mg groups took 2 capsules, 4 capsules and 6 capsules of the study drug, respectively, and were followed up for 7 days (inclusive of the date of administration).

2. Multiple-Dose Period

In the Dose-Escalation Cohort, subjects in each group entered the 84-day Multiple-Dose Period after the Single-Dose Period. However, subjects in the 240-mg group continued the study treatment at a reduced dose of 160 mg in the subsequent periods starting with the Multiple-Dose Period. Subjects in the 80-mg and 160-mg groups daily received 2 capsules and 4 capsules of the study drug, respectively. In the Expansion Cohort, the study drug administration was started at a dose of 160 mg (4 capsules) in the Multiple-Dose Period.

3. Long-Term Dosing Period

After the Multiple-Dose Period, all subjects in each group entered the Long-Term Dosing Period, when they received the study drug at the dose assigned to their treatment group. Subjects in the 80-mg group, however, were allowed to receive an increased dose of 160 mg at the discretion of the investigator or sub-investigator once the first subject in the Expansion Cohort started study treatment at 160 mg. The subjects in the Long-Term Dosing Period remained on study treatment until one of the discontinuation criteria was met (up to marketing approval).

Interruption of Study Drug

If further continuation of treatment with the study drug became difficult because of an adverse event (AE), the investigator or sub-investigator suspended the treatment. If the resumption of the study treatment was still difficult after an interruption of 15 days or longer, discontinuation of the study for the patient was considered. If resolution of the AE or an apparent reduction in the severity was confirmed after interruption of the study treatment and the investigator or sub-investigator considered that the resumption of the study treatment was medically possible, the patient received the study drug again.

Duration of Treatment (or Duration of Study, if applicable): Single-Dose Period, 1 day; Multiple-Dose Period, 84 days; and Long-Term Dosing Period, until one of the discontinuation criteria was met.

Reference Product, Dose and Mode of Administration, Batch Numbers: Not applicable

Criteria for Evaluation: The following endpoints were evaluated.

Efficacy:

Primary Endpoint

- Tumor response by Day 85 (best overall response from screening to Day 85 [or Early Termination]) as defined by RECIST

Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: To be determined		
Name of Active Ingredient: MDV3100		

Secondary endpoints

- Serum PSA response rate (proportion of subjects with ≥50% decline in serum PSA from baseline);
- PSA response rate at maximum response;
- Changes in serum PSA level;
- Changes in circulating tumor cell (CTC) counts;
- Changes in serum bone-specific alkaline phosphatase (B-ALP) and urinary N-telopeptide (NTx);
- Changes in serum testosterone and serum sex hormone binding globulin (SHBG) levels;
- Frequency and timing of disease progression (as determined by radiographic examination and serum PSA).

Pharmacokinetics: Plasma concentration of MDV3100, plasma concentrations of metabolites (MDPC0001 and MDPC0002), and urinary concentration of MDV3100.

Safety: AEs, laboratory values, vital signs, body weight and 12-lead electrocardiogram (ECG; including QT evaluation).

Statistical Methods:

Efficacy: In the primary analysis of the primary endpoint, the number and percentage of subjects with a best overall response of CR or PR (response rate) by Day 85 were calculated. In the secondary analysis of the primary endpoint, the number and percentage of subjects with a best overall response of CR, PR or SD (disease control rate) by Day 85 were calculated, and the response rate and the disease control rate by the last day in the Long-Term Dosing Period were calculated. For the secondary endpoints, summary statistics of measured values and the percent change from baseline were calculated at each time point. In addition, the proportion of subjects with at least 25%, 30%, 50% or 90% decline in serum PSA from baseline were summarized for each time point. For CTC, the number and percentage of subjects with favorable and unfavorable data were summarized for each time point. For disease progression determined by radiographic examination, serum PSA and overall survival, using the Kaplan-Meier method with disease progression as the event, the cumulative disease progression rate was estimated.

Pharmacokinetics: Plasma and urine analyte concentrations were summarized for each time point. PK parameters for MDV3100, MDPC0001, MDPC0002 and the sum of MDV3100 and MDPC0002 (MDV3100+MDPC0002) were calculated from the plasma concentration-time data and summarized. In addition, assessments of such as dose-proportionality, dose-linearity, accumulation and steady state were performed.

Safety: AEs observed after the first study drug administration during the study period (treatment-emergent AEs; TEAEs) were analyzed and summarized using Medical Dictionary for Regulatory Activities (MedDRA) Version 14.1, system organ class and preferred term. TEAEs that were categorized as either possibly related or probably related to the study drug were defined as drug-related TEAEs whose relationship to the study drug could not be ruled out. Clinical laboratory data, vital signs and ECGs were primarily analyzed for the Expansion Cohort. For laboratory data, continuous variables were summarized with descriptive statistics of measured values and categorical variables were summarized with frequencies and percentage. For vital signs, continuous variables

Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: To be determined		
Name of Active Ingredient: MDV3100		

were summarized with descriptive statistics of measured values and potentially clinically significant abnormalities were summarized with frequencies and percentage. For ECG data, continuous QT variables were summarized with descriptive statistics and categorical QT variables were summarized with frequencies and percentage. In addition, number and percentage of subjects with normal, not clinically significant abnormal, and clinically significant abnormal results of the ECG at each time point were calculated.

Summary of Results/Conclusions:

Disposition of Subjects and Analysis Sets:

For the Dose-Escalation Cohort, 9 of the 10 patients who gave written informed consent were registered; 3 patients were assigned to each of the 80-, 160- and 240-mg groups [Figure 1]. All of the 9 patients were treated with the study drug at the dose allocated for their treatment group in the Single-Dose Period. In the Multiple-Dose Period, 6 patients who were assigned to the 80- and 160-mg groups were treated at the dose allocated for their treatment group, and 3 patients who were assigned to the 240-mg group were treated at 160 mg. One patient in the 240-mg group terminated the study because of worsening of disease during the Multiple-Dose Period. Thus, 8 patients entered the Long-Term Dosing Period. The patients who were assigned to 80-mg group started the treatment in the Long-Term Dosing Period at 80 mg, and the dose was increased to 160 mg during the Long-Term Dosing Period. Five patients who were assigned to the 160- or 240-mg groups were treated at 160 mg. All 9 patients in the Dose-Escalation Cohort discontinued the study treatment because of worsening of disease (7 patients), because of AEs (1 patient) or withdrawal by subject (1 patient).

All 9 patients in the Dose-Escalation Cohort were included in the FAS, SAF and PKAS. Seven patients (2, 3 and 2 patients in the 80-, 160- and 240-mg groups, respectively) in the Dose-Escalation Cohort were excluded from the PPS because of lack of data for the primary efficacy endpoint.

For the Expansion Cohort, 38 of the 56 patients who gave written informed consent were finally registered; all of the registered patients were treated with the study drug at a dose of 160 mg throughout the study. In the Multiple-Dose Period, 12 patients terminated the study because of AEs (5 patients), worsening of disease (5 patients) or withdrawal by the patient (2 patients). Of 38 patients enrolled in the Expansion Cohort, 38 patients discontinued the study; enzalutamide treatment was discontinued in 38 patients due to worsening of disease (24 patients), adverse event (10 patients), withdrawal by subject (2 patients) or other reason (2 patients), whereas 2 patients who discontinued the study treatment because of other reason switched from study drug to commercial enzalutamide at study termination.

All 38 patients in the Expansion Cohort were included in the FAS, PPS, SAF and PKAS.

Demographics and Other Baseline Characteristics:

In the Dose-Escalation Cohort (n=3/dose), there were no notable differences among the 3 dose groups, except for the following: patients in the 80-mg group were younger, patients in the 160-mg group all had metastatic

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Name of Finished Product: To be determined		
Name of Active Ingredient: MDV3100		

prostate cancer at initial diagnosis [Table 1]. In all groups, the range of PSA at baseline varied widely. The age ranged from 62 to 86 years, and weight ranged from 49.2 to 88.9 kg.

In the Expansion Cohort (n=38), the age ranged from 50 to 85 years, and the weight ranged from 49.2 to 93.0 kg.

No remarkable differences were observed in the demographics and other baseline characteristics between the Dose-Escalation Cohort and Expansion Cohort.

Efficacy Results:

- The best overall response rate (the combined response rate for CR and PR) by Day 85 was 5.3% (2/38, 95% CI: 0.6%, 17.7%), and the disease control rate (the combined rate for CR, PR and SD) by Day 85 was 47.4% (18/38, 95% CI: 31.0%, 64.2%), when evaluated by the RECIST assessment committee and the investigators [Table 2]. There was no patient who experienced CR and no remarkable differences in the best overall response and disease control rate were found between any of the specific subgroups that were analyzed.
- The best overall response rate (the combined response rate for CR and PR) by Day 85 was 7.9% (3/38, 95% CI: 1.7%, 21.4%), and the disease control rate (the combined rate for CR, PR and SD) by Day 85 was 50.0% (19/38, 95% CI: 33.4%, 66.6%), when evaluated by the investigators. There was 1 patient who experienced CR when evaluated by the investigator.
- Maximal PSA decline (≥50% from baseline) was observed in 28.9% (11/38, 95% CI: 15.4%, 45.9%) of the patients [Table 3].
- Of the 18 patients with unfavorable CTC counts at baseline, 9 patients had post-baseline CTC data. Of those, MDV3100 therapy was associated with conversion to favorable CTC counts in 5 patients who had previously received chemotherapy.
- Serum B-ALP levels did not change markedly in the majority of patients, while urinary NTx levels were variable and high in many patients and fluctuated during the study period.
- Serum testosterone levels remained within castration level (<0.50 ng/mL) and serum SHBG increased from baseline in the majority of patients during the study period.
- The median time to serum PSA progression, radiographic disease progression and death (overall survival) were 122.0 days (95% CI: 86.0, 198.0), 163.0 days (95% CI: 85.0, 253.0) and 345.0 days (95% CI: 222.0, not estimated), respectively.

Pharmacokinetic Results:

- In the Single-Dose Period, plasma MDV3100 concentrations increased rapidly after dosing with a median t_{max} ranging from 1.083 to 2.100 h and after t_{max} decreased slowly with a mean $t_{1/2}$ ranging from 113.251 to 202.454 h across the doses [Figure 3, Table 4]. The mean C_{max}, AUC_{7d} and AUC_{inf} as well as C_{24h} and AUC_{24h} increased with dose. The means for both CL/F and V_z/F were comparable across the doses. Dose-proportionality was confirmed ($P<0.05$) for C_{max}, AUC_{7d} and AUC_{inf} and the data suggested dose-linearity.

Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: To be determined		
Name of Active Ingredient: MDV3100		

A small amount of MDV3100 (<0.1% of the dose) was measured in urine from 2 patients in the 240-mg group but not in the lower dose groups.

- In the Single-Dose Period, plasma MDPC0001 and MDPC0002 concentrations increased gradually with time after administration of MDV3100 [Table 5, Table 6]. The mean molecular weight-corrected MPR (ratio to MDV3100) for AUC_{7d} ranged from 0.092 to 0.174 and 0.228 to 0.391 for MDPC0001 and MDPC0002, respectively. For MDV3100+MDPC0002, the mean plasma concentrations versus time profiles were similar to those for MDV3100 [Table 7]. Dose-proportionality was confirmed ($P<0.05$) for the C_{max} and AUC_{7d} for both metabolites, and the data suggested dose-linearity.
- In the Multiple-Dose Period and Long-Term Dosing Period, the median t_{max} for plasma MDV3100 concentrations on Day 85 in the 160-mg group of the Dose-Escalation Cohort was comparable to that (on Day S1) in the Single-Dose Period [Table 8]. The mean C_{max}, C_{24h} and AUC_{24h} on Day 85 and Ave-SS-C_{trough} increased with dose. The mean PTR (C_{max}/C_{24h}) ranged from 1.224 to 1.378 and the mean CL/F ranged from 0.4710 to 0.5324 L/h. The mean accumulation index (ratio of AUC_{24h} on Day 85 to Day S1) and the accumulation ratio (ratio of C_{24h} on Day 85 to Day S1) ranged from 8.000 to 10.765 and 8.054 to 9.739, respectively. The mean C_{trough} increased until around Day 29 and then became almost constant, suggesting that it took approximately 29 days to reach steady state.
- In the Multiple-Dose Period and Long-Term Dosing Period, the median t_{max} for plasma MDPC0001 and MDPC0002 concentrations on Day 85 in the 160-mg group of the Dose-Escalation Cohort was 1.000 h and 0.500 h, respectively [Table 9]. The mean MPR for C_{max} on Day 85 was 0.485 and 0.941, and that for AUC_{24h} on Day 85 was 0.471 and 0.894 for MDPC0001 and MDPC0002, respectively. The mean PTR was 1.151 for MDPC0001 and 1.183 for MDPC0002. The mean accumulation index and accumulation ratio were 82.093 and 50.403 for MDPC0001, and 186.922 and 96.443 for MDPC0002. The mean C_{trough} of MDPC0001 and MDPC0002 increased until Days 29 to 57 and then became almost constant. The mean Ave-SS-C_{trough} was 8.281 and 12.968 µg/mL for MDPC0001 and MDPC0002, respectively. For MDV3100+MDPC0002 concentrations, the median t_{max} on Day 85 was 0.500 h; the mean C_{max}, C_{24h} and AUC_{24h} on Day 85 were 29.296 µg/mL, 25.361 µg/mL and 640.861 µg·h/mL, respectively. The mean PTR was 1.164. The mean accumulation index and accumulation ratio were 19.058 and 17.163, respectively. The mean C_{trough} increased until around Day 29 and then became almost constant. The mean Ave-SS-C_{trough} was 26.236 µg/mL.
- Results in the Expansion Cohort were generally consistent with those in the 160-mg group of the Dose-Escalation Cohort.

Safety Results:

- A total of 1 death (unknown cause of death, attributed to drowning) was reported in the Dose-Escalation Cohort (11.1%, 1 of 9 patients) and 1 event resulting in death (disseminated intravascular coagulation) in the Expansion Cohort (2.6%, 1 of 38 patients) [Table 10]. Both events were considered unrelated to the study drug.

Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: To be determined		
Name of Active Ingredient: MDV3100		

- A total of 38 episodes of serious TEAEs were reported in 3 of 9 patients (33.3%) in the Dose-Escalation Cohort when analyzed during both the Single-Dose Period and subsequent Multiple-Dose Period and in 13 of 38 patients (34.2%) in the Expansion Cohort [Table 10]. Overall, serious TEAEs of the SOC "neoplasms benign, malignant and unspecified (incl cysts and polyps)" were the most common (7 episodes). Drug-related serious TEAEs were reported only in the Expansion Cohort; the incidence was 10.5%.
- TEAEs occurred in all 9 patients in the Dose-Escalation Cohort when analyzed during both the Single-Dose Period and subsequent Multiple-Dose Period and in 36 of 38 (94.7%) patients in the Expansion Cohort [Table 11 and Table 12]. The most common TEAEs (incidence ≥10%) in the Expansion Cohort were weight decreased (47.4%); decreased appetite (28.9%); constipation (26.3%); cancer pain (21.1%); hypertension (18.4%); electrocardiogram QT prolonged (15.8%); nausea, nasopharyngitis, somnolence, haematuria and rash (13.2%); anaemia, fatigue, pyrexia, blood potassium decreased, tumour pain and hydronephrosis (10.5%).
- The incidence of drug-related TEAEs was 77.8% in the Dose-Escalation Cohort, and 63.2% in the Expansion Cohort [Table 13]. The most common drug-related TEAEs (incidence ≥10%) in the Expansion Cohort were constipation (15.8%); electrocardiogram QT prolonged, weight decreased and hypertension (13.2%); fatigue and decreased appetite (10.5%).
- The incidence of Grade 3 or higher TEAEs was 66.7% in the Dose-Escalation Cohort, and 63.2% in the Expansion Cohort. The incidence of drug-related Grade 3 or higher TEAEs was 55.6% in the Dose-Escalation Cohort, and 36.8% in the Expansion Cohort.
- The incidence of TEAEs leading to permanent discontinuation was 11.1% in the Dose-Escalation Cohort, and 26.3% in the Expansion Cohort [Table 15].
- Seizure did not occur in the patients in any cohort or group.
- The results for subgroup analysis of TEAEs included the findings that the incidence of weight decreased was 63.0% (17/27) in patients of age <75 years, while only 9.1% (1/11) in patients of age ≥75 years; and that the incidence of constipation was 34.5% (10/29) in patients with a high total Gleason score at initial diagnosis (8 to 10), while 0% (0/8) in patients with a medium score (5 to 7).
- Common abnormal or clinically significant laboratory findings regarded as TEAEs in the Expansion Cohort were haemoglobin decreased (Grade 1 or 2), blood albumin decreased (Grade 2) and blood potassium decreased (Grade 2 or 3), each of which was considered unrelated to the study drug by the investigator.
- Abnormalities in vital signs found in the Expansion Cohort were decrease of systolic blood pressure (5.3%), decrease of diastolic blood pressure, increase of pulse rate and decrease of pulse rate (2.6% each) (End-of-Text Table B.12.6.3.2). Blood pressure increased was reported as a TEAE (Grade 3) in 2 patients (5.3%), one of which was considered drug related (End-of-Text Table B.12.6.1.4.1 and Table B.12.6.1.6). No marked changes in the median for ECG parameters were found during the study period (the median QTcF ranged from 388.0 to 436.0 ms; the median changes from baseline QTcF ranged from −7.0 to 13.0 ms) (End-of-Text Table B.12.6.4.2); however, electrocardiogram QT prolonged was reported as a TEAE in 6 patients (15.8%) in the Expansion Cohort and considered related to the study drug in 5 patients (13.2%) by

Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: To be determined		
Name of Active Ingredient: MDV3100		

the investigator, including 1 event of Grade 3 severity (End-of-Text Table B.12.6.1.5.1 and Table B.12.6.1.6).

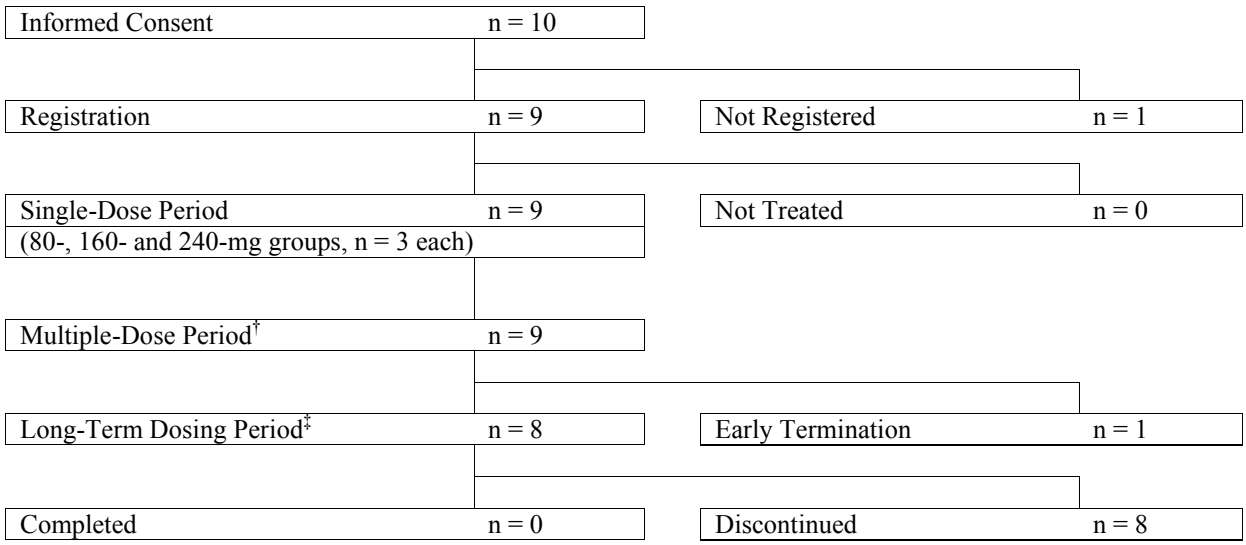
CONCLUSIONS:

- MDV3100 had antitumor activity in terms of best overall response by Day 85 and serum PSA level in post-chemo CRPC patients when orally administered at a dose of 160 mg once daily.
- MDV3100 was absorbed rapidly after oral administration and the PK of MDV3100 was dose-proportional in the dose ranging from 80 to 240 mg. The mean $t_{1/2}$ of MDV3100 was approximately 113 to 202 h, thus taking approximately 29 days to reach steady state. The mean accumulation index of MDV3100 was approximately 8 to 11, and the mean PTR was approximately 1.2 to 1.4.
- Overall, MDV3100 was considered safe and well tolerated in CRPC patients when orally administered at a dose of 160 mg once daily for long term more than 12 weeks.

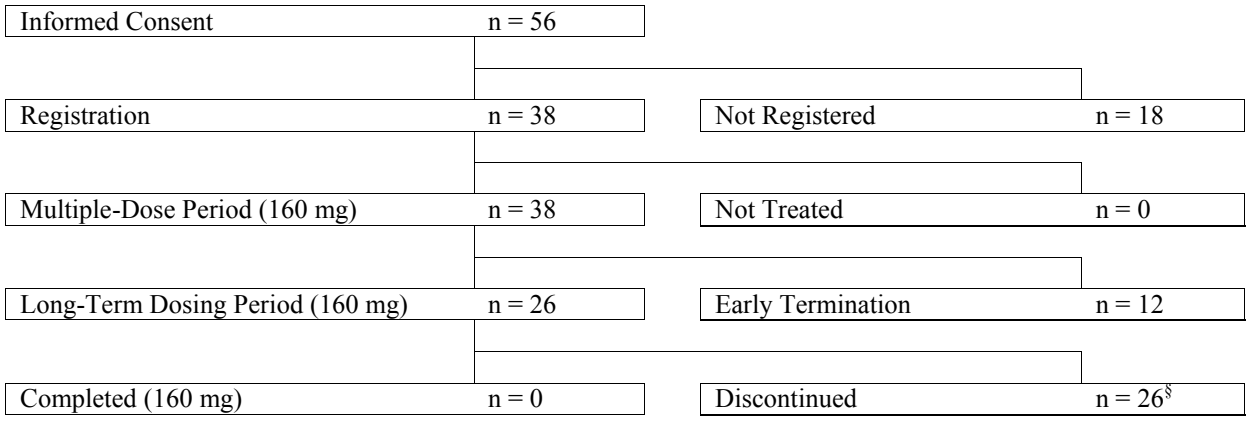
Date of Report: 9 Feb 2015

Figure 1: Disposition of Subjects

Dose-Escalation Cohort



Expansion Cohort



† All patients in the 240-mg group received MDV3100 at a dose of 160 mg after the Single-Dose Period.
‡ For patients in the 80-mg group, the dose of MDV3100 was increased to 160 mg during the Long-Term Dosing Period.
§ Two patients switched from the study drug to commercial enzalutamide at the termination of the study treatment.
Source: Tables A.12.1.1.1, A.12.1.1.2, A.12.1.1.4, B.12.1.1.1, A.12.2.1.1, B.12.1.1.2, B.12.1.1.4 and Appendix B.13.2.1.2

Table 1: Summary of Demographics and Other Baseline Characteristics: FAS

Demographics/Characteristics		Dose-Escalation Cohort				Expansion Cohort
		80 mg (n = 3)	160 mg (n = 3)	240 mg (n = 3)	Total (n = 9)	160 mg (n = 38)
Age (years)	Mean (Std)	67.0 (5.0)	79.0 (6.1)	74.0 (2.6)	73.3 (6.7)	70.3 (7.7)
	Median	67.0	76.0	73.0	73.0	71.5
	Range	62 - 72	75 - 86	72 - 77	62 - 86	50 - 85
	<65[†]	1 (33.3%)	0	0	1 (11.1%)	11 (28.9%)
	65 to 74[†]	2 (66.7%)	0	2 (66.7%)	4 (44.4%)	16 (42.1%)
	≥75[†]	0	3 (100.0%)	1 (33.3%)	4 (44.4%)	11 (28.9%)
Height (cm)	Mean (Std)	166.23 (3.09)	168.63 (5.29)	164.37 (7.48)	166.41 (5.18)	165.81 (6.74)
	Median	164.50	167.50	166.00	166.00	165.70
	Range	164.4 - 169.8	164.0 - 174.4	156.2 - 170.9	156.2 - 174.4	153.4 - 181.0
Weight (kg)	Mean (Std)	76.10 (6.83)	73.17 (11.56)	67.37 (20.06)	72.21 (12.67)	66.88 (8.96)
	Median	73.20	68.10	64.00	71.20	65.70
	Range	71.2 - 83.9	65.0 - 86.4	49.2 - 88.9	49.2 - 88.9	49.2 - 93.0
Body Mass Index (kg/m^2)	Mean (Std)	27.50 (1.44)	25.62 (2.42)	24.61 (5.27)	25.91 (3.25)	24.32 (2.90)
	Median	27.08	24.27	23.23	26.31	24.27
	Range	26.3 - 29.1	24.2 - 28.4	20.2 - 30.4	20.2 - 30.4	18.7 - 34.2
Body Surface Area (m^2)	Mean (Std)	1.84 (0.09)	1.83 (0.16)	1.73 (0.27)	1.80 (0.17)	1.74 (0.13)
	Median	1.80	1.77	1.71	1.78	1.74
	Range	1.8 - 2.0	1.7 - 2.0	1.5 - 2.0	1.5 - 2.0	1.5 - 2.0
ECOG P.S.[†]	Grade 0	3 (100.0%)	3 (100.0%)	2 (66.7%)	8 (88.9%)	25 (65.8%)
	Grade 1	0	0	1 (33.3%)	1 (11.1%)	13 (34.2%)
Total Gleason Score[‡] at Initial Diagnosis[†]	Low: 2-4	0	0	0	0	0
	Medium: 5-7	0	0	0	0	8 (21.1%)
	High: 8-10	3 (100.0%)	3 (100.0%)	3 (100.0%)	9 (100.0%)	29 (76.3%)
	Unknown	0	0	0	0	1 (2.6%)
Clinical Tumor Stage (T)[§] at Initial Diagnosis[†]	TX	0	0	1 (33.3%)	1 (11.1%)	1 (2.6%)
	T0	0	0	0	0	0
	T1	0	0	0	0	0
	T2	0	0	1 (33.3%)	1 (11.1%)	10 (26.3%)
	T3	3 (100.0%)	2 (66.7%)	1 (33.3%)	6 (66.7%)	16 (42.1%)
	T4	0	1 (33.3%)	0	1 (11.1%)	10 (26.3%)
	Unknown	0	0	0	0	1 (2.6%)
Clinical Lymph Node Stage at Initial Diagnosis[†]	NX	1 (33.3%)	0	1 (33.3%)	2 (22.2%)	1 (2.6%)
	N0	0	1 (33.3%)	2 (66.7%)	3 (33.3%)	14 (36.8%)
	N1	2 (66.7%)	2 (66.7%)	0	4 (44.4%)	22 (57.9%)
	Unknown	0	0	0	0	1 (2.6%)
Distant Metastasis (M)[§] at Iinitial Diagnosis[†]	MX	0	0	0	0	1 (2.6%)
	M0	1 (33.3%)	0	2 (66.7%)	3 (33.3%)	17 (44.7%)
	M1	2 (66.7%)	3 (100.0%)	1 (33.3%)	6 (66.7%)	19 (50.0%)
	Unknown	0	0	0	0	1 (2.6%)
Previous Disease[†]	Yes	1 (33.3%)	1 (33.3%)	0	2 (22.2%)	11 (28.9%)
	No	2 (66.7%)	2 (66.7%)	3 (100.0%)	7 (77.8%)	27 (71.1%)
Previous Nervous System Disorders[†]	Yes	0	0	0	0	0
	No	3 (100.0%)	3 (100.0%)	3 (100.0%)	9 (100.0%)	38 (100.0%)
Concomitant Disease[†]	Yes	3 (100.0%)	3 (100.0%)	3 (100.0%)	9 (100.0%)	38 (100.0%)
	No	0	0	0	0	0
Concomitant Nervous System Disorders[†]	Yes	0	0	0	0	10 (26.3%)
	No	3 (100.0%)	3 (100.0%)	3 (100.0%)	9 (100.0%)	28 (73.7%)
Anti-androgen Withdrawal Syndrome[†]	Yes	0	0	0	0	4 (10.5%)
	No	3 (100.0%)	3 (100.0%)	3 (100.0%)	9 (100.0%)	34 (89.5%)

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Demographics/Characteristics		Dose-Escalation Cohort				Expansion Cohort
		80 mg (n = 3)	160 mg (n = 3)	240 mg (n = 3)	Total (n = 9)	160 mg (n = 38)
Stage of Prostate Cancer†, §	Localized	0	0	1 (33.3%)	1 (11.1%)	6 (15.8%)
	Locally Advanced	1 (33.3%)	0	1 (33.3%)	2 (22.2%)	11 (28.9%)
	Metastatic	2 (66.7%)	3 (100.0%)	1 (33.3%)	6 (66.7%)	19 (50.0%)
	Not Classifiable	0	0	0	0	2 (5.3%)
PSA at Baseline (ng/mL)	Mean (Std)	1420.80 (2432.84)	461.97 (652.03)	21.71 (15.43)	634.82 (1403.52)	174.94 (307.97)
	Median	21.60	162.00	19.30	21.60	65.80
	Range	10.8 - 4230.0	13.9 - 1210.0	7.6 - 38.2	7.6 - 4230.0	2.2 - 1330.0
Duration of Disease at Screening (months)	Mean (Std)	40.78 (3.76)	49.22 (23.14)	52.08 (36.37)	47.36 (22.23)	63.11 (38.15)
	Median	40.27	39.93	32.00	39.93	52.83
	Range	37.3 - 44.8	32.2 - 75.6	30.2 - 94.1	30.2 - 94.1	17.7 - 164.8
	<60†	3 (100.0%)	2 (66.7%)	2 (66.7%)	7 (77.8%)	20 (52.6%)
	≥60†	0	1 (33.3%)	1 (33.3%)	2 (22.2%)	18 (47.4%)

† Number (%) of patients
‡ Gleason DF, 1992
§ Classified using the TNM classification [Sobin LH & Wittekind C, 2003] as follows: Localized, T1/2 and (NX or N0) and M0; Locally Advanced, T3/4 and (NX or N0) and M0 or N1 and M0; Metastatic, M1; Not Classifiable, others
Source: Tables A.12.1.2.1 and B.12.1.2.1

Table 2: Best Overall Responses by Day 85: FAS

Best Overall Response	Evaluation by RECIST Assessment Committee and Investigator† (n = 38)	Evaluation by Investigator (n = 38)
Complete Response (CR)	0	1 (2.6%)
Partial Response (PR)	2 (5.3%)	2 (5.3%)
Stable Disease (SD)	16 (42.1%)	16 (42.1%)
Progressive Disease (PD)	16 (42.1%)	15 (39.5%)
Not Evaluated (NE)	4 (10.5%)	4 (10.5%)
CR or PR (response rate)	2 (5.3%)	3 (7.9%)
Response rate, 90% CI‡	0.9%, 15.7%	2.2%, 19.2%
Response rate, 95% CI‡	0.6%, 17.7%	1.7%, 21.4%
CR or PR or SD (disease control rate)	18 (47.4%)	19 (50.0%)
Disease control rate, 90% CI‡	33.3%, 61.8%	35.7%, 64.3%
Disease control rate, 95% CI‡	31.0%, 64.2%	33.4%, 66.6%

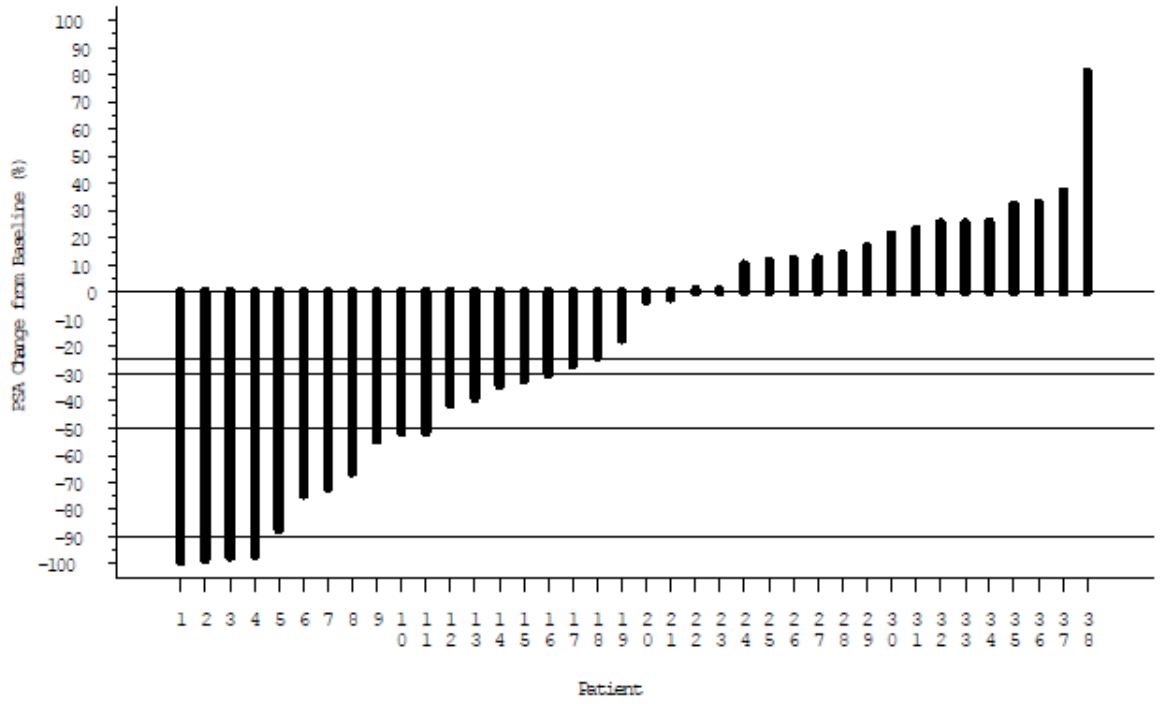
Number (%) of patients
Tumor response (overall response) for each patient was assessed by the investigator, subsequently evaluated by an independent RECIST assessment committee when the investigator assessed that a patient had been accomplished CR or PR.
† When there were evaluation data from both the RECIST committee and investigator, RECIST assessment committee data were adopted.
‡ Based on exact binomial confidence interval (Clopper-Pearson)
Source: Tables B.12.3.1.1.1.1 and B.12.3.1.1.2.1

Table 3: Best PSA Response at Time of Nadir: FAS

Response	MDV3100 160 mg/day (n = 38)
≥25% decline from baseline	17/38 (44.7%)
≥30% decline from baseline	15/38 (39.5%)
≥50% decline from baseline	11/38 (28.9%)
≥90% decline from baseline	4/38 (10.5%)

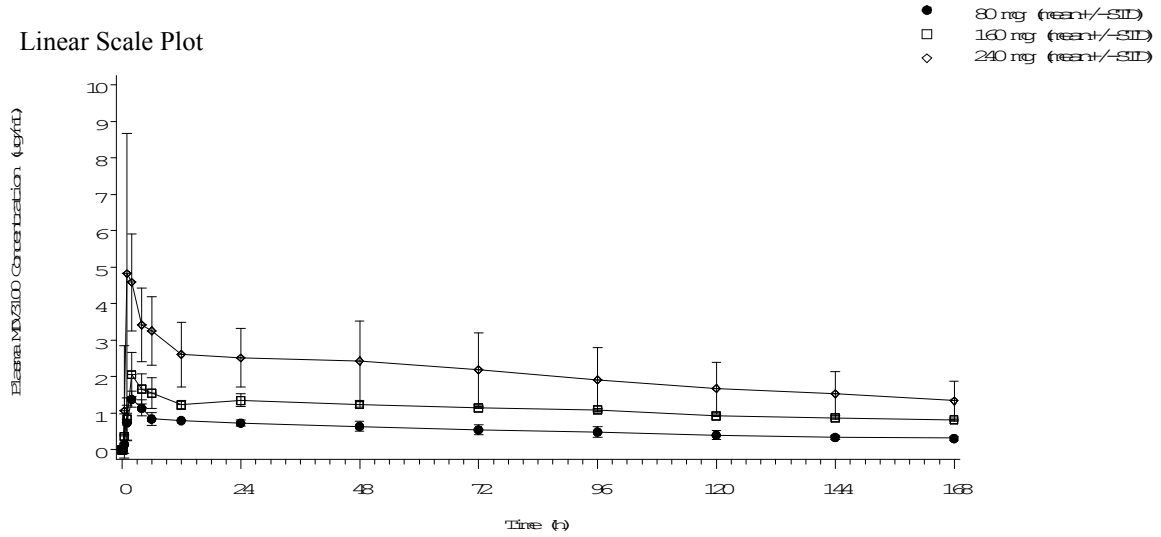
Number of patients/n (%)
Only patients who had both baseline and post-baseline assessments are included and visit windows are not considered in this analysis.
Source: Tables B.12.3.2.1.3.1, B.12.3.2.1.3.2, B.12.3.2.1.3.3 and B.12.3.2.1.3.4

Figure 2: Waterfall Plot of Maximum Percent Change from Baseline of Serum PSA: FAS



Only patients who had both baseline and post-baseline assessments are included and visit windows are not considered in this analysis.
Source: Figure B.12.3.1.6

Figure 3: Mean plasma MDV3100 Concentrations Versus Time Profiles for the Single-Dose Period: PKAS



Note: n = 3 in each group.
Source: Figure A.12.4.1.1

Table 4: Plasma MDV3100 Pharmacokinetic Parameters in the Single-Dose Period: PKAS

Parameter		80 mg (n = 3)	160 mg (n = 3)	240 mg (n = 3)
C_{max} (µg/mL)	Mean	1.421	2.169	5.717
	Std	0.1728	0.5512	2.3015
t_{max} (h)	Median	2.100	2.000	1.083
	Min - Max	1.95 - 3.95	1.83 - 3.97	0.92 - 2.00
C_{24h} (µg/mL)	Mean	0.733	1.350	2.518
	Std	0.0896	0.1763	0.8068
AUC_{24h} (µg·h/mL)	Mean	19.171	32.084	69.351
	Std	2.1443	3.7724	22.9821
AUC_{7d} (µg·h/mL)	Mean	82.291	165.147	315.645
	Std	15.9793	7.0620	127.2679
AUC_{inf} (µg·h/mL)	Mean	141.179	424.782	652.529
	Std	25.9371	26.9145	268.1273
%AUC (%)	Mean	36.276	56.246	44.963
	Std	3.0360	3.7017	9.3137
$t_{1/2}$ (h)	Mean	113.251	202.454	151.182
	Std	10.7106	25.4489	34.6440
CL/F (L/h)	Mean	0.5796	0.3777	0.4293
	Std	0.10666	0.02449	0.22586
V_z/F (L)	Mean	94.3922	109.8675	88.7829
	Std	17.70389	9.96401	32.63580

Source: Table A.12.4.4.1

Table 5: Plasma MDPC0001 Pharmacokinetic Parameters in the Single-Dose Period: PKAS

Parameter		80 mg (n = 3)	160 mg (n = 3)	240 mg (n = 3)
C_{max} (µg/mL)	Mean	0.079	0.287	0.219
	Std	0.0349	0.2006	0.0800
t_{max} (h)	Median	96.050	144.100	96.000
	Min - Max	96.05 - 119.88	120.00 - 168.03	96.00 - 168.07
C_{24h} (µg/mL)	Mean	0.037	0.155	0.126
	Std	0.0082	0.1006	0.0498
AUC_{24h} (µg·h/mL)	Mean	0.699	2.295	2.134
	Std	0.1217	1.5265	0.5769
AUC_{7d} (µg·h/mL)	Mean	8.230	28.406	24.943
	Std	3.3732	18.7578	9.2008

Source: Table A.12.4.4.2

Table 6: Plasma MDPC0002 Pharmacokinetic Parameters in the Single-Dose Period: PKAS

Parameter		80 mg (n = 3)	160 mg (n = 3)	240 mg (n = 3)
C_{max} (µg/mL)	Mean	0.358	0.463	0.952
	Std	0.0298	0.0490	0.3838
t_{max} (h)	Median	167.550	168.000	144.000
	Min - Max	120.10 - 167.92	167.25 - 168.03	118.08 - 167.92
C_{24h} (µg/mL)	Mean	0.131	0.131	0.270
	Std	0.0372	0.0347	0.0711
AUC_{24h} (µg·h/mL)	Mean	1.677	1.661	3.610
	Std	0.3890	0.4445	0.8461
AUC_{7d} (µg·h/mL)	Mean	31.300	36.535	82.767
	Std	6.7125	4.9598	34.9696

Source: Table A.12.4.4.3

Table 7: Plasma MDV3100+MDPC0002 Pharmacokinetic Parameters in the Single-Dose Period: PKAS

Parameter		80 mg (n = 3)	160 mg (n = 3)	240 mg (n = 3)
C_{max} (µg/mL)	Mean	1.445	2.180	5.743
	Std	0.1496	0.5487	2.2953
t_{max} (h)	Median	2.100	2.000	1.083
	Min - Max	1.95 - 3.95	1.83 - 3.97	0.92 - 2.00
C_{24h} (µg/mL)	Mean	0.864	1.482	2.788
	Std	0.1268	0.1987	0.8651
AUC_{24h} (µg·h/mL)	Mean	20.848	33.745	72.961
	Std	2.4802	4.0636	23.5615
AUC_{7d} (µg·h/mL)	Mean	113.591	201.683	398.411
	Std	22.4780	9.6237	160.3178

Source: Table A.12.4.4.4

Table 8: Plasma MDV3100 Pharmacokinetic Parameters on Day 85: PKAS

Parameter		Dose-Escalation Cohort			Expansion Cohort
		80 mg (n = 3)	160 mg (n = 3)	240 mg† (n = 3)	160 mg (n = 38)
C_{max} (µg/mL)	n	3	3	2	25
	Mean	8.006	16.072	14.400	14.501
	Std	2.6071	2.1337	2.5394	2.9339
t_{max} (h)	n	3	3	2	25
	Median	0.883	1.867	1.500	1.000
	Min - Max	0.33 - 1.98	0.00 - 2.10	1.08 - 1.92	0.00 - 22.92
C_{24h} (µg/mL)	n	3	3	2	21
	Mean	5.787	13.196	11.123	11.219
	Std	0.8776	2.2247	2.5471	2.0876
AUC_{24h} (µg·h/mL)	n	3	3	2	25
	Mean	152.169	346.828	308.677	296.141
	Std	20.4747	57.9969	66.9495	55.3445
CL/F (L/h)	n	3	3	2	25
	Mean	0.5324	0.4710	0.5308	0.5574
	Std	0.07452	0.08658	0.11513	0.09719
PTR‡	n	3	3	2	21
	Mean	1.378	1.224	1.303	1.258
	Std	0.3486	0.0556	0.0700	0.1693
Accumulation Index§	n	3	3	NA	NA
	Mean	8.000	10.765	NA	NA
	Std	1.3450	0.6016	NA	NA
Accumulation Ratio††	n	3	3	NA	NA
	Mean	8.054	9.739	NA	NA
	Std	2.0669	0.4180	NA	NA

NA = not applicable
† All patients in the 240-mg group received MDV3100 at a dose of 160 mg after the Single-Dose Period.
‡ Peak-to-trough ratio; calculated as C_{max}/C_{24h}
§ Ratio of AUC_{24h} on Day 85 to Day S1
†† Ratio of C_{24h} on Day 85 to Day S1
Source: Tables A.12.4.5.1 and B.12.4.5.1

Table 9: Plasma MDV3100 Metabolite Pharmacokinetic Parameters on Day 85: PKAS

Parameter		Dose-Escalation Cohort 160 mg (n = 3)			Expansion Cohort 160 mg (n = 38)		
		MDPC0001	MDPC0002	MDV3100+ MDPC0002	MDPC0001	MDPC0002	MDV3100+ MDPC0002
C_{max} (µg/mL)	n	3	3	3	25	25	25
	Mean	7.865	14.328	29.296	7.791	13.877	27.487
	Std	3.9957	1.6487	1.9246	6.4485	2.5741	4.2632
t_{max} (h)	n	3	3	3	25	25	25
	Median	1.000	0.500	0.500	1.000	0.000	0.583
	Min - Max	0.00 - 1.02	0.00 - 2.10	0.22 - 2.10	0.00 - 23.83	0.00 - 22.92	0.00 - 22.92
C_{24h} (µg/mL)	n	3	3	3	21	21	21
	Mean	7.036	12.165	25.361	6.407	12.931	24.149
	Std	3.8434	0.6201	2.7255	5.2694	2.3458	3.9910
AUC_{24h} (µg·h/mL)	n	3	3	3	25	25	25
	Mean	166.040	294.033	640.861	164.478	293.182	589.324
	Std	86.7065	24.2831	58.9226	143.1806	47.7267	89.6665
PTR†	n	3	3	3	21	21	21
	Mean	1.151	1.183	1.164	1.139	1.073	1.129
	Std	0.0953	0.1829	0.1361	0.1463	0.0707	0.0864
Accumulation Index‡	n	3	3	3	NA	NA	NA
	Mean	82.093	186.922	19.058	NA	NA	NA
	Std	23.1882	56.3110	1.2292	NA	NA	NA
Accumulation Ratio§	n	3	3	3	NA	NA	NA
	Mean	50.403	96.443	17.163	NA	NA	NA
	Std	11.9490	22.5741	0.6055	NA	NA	NA

NA = not applicable
† Peak-to-trough ratio; calculated as C_{max}/C_{24h}
‡ Ratio of AUC_{24h} on Day 85 to Day S1
§ Ratio of C_{24h} on Day 85 to Day S1
Source: Tables A.12.4.5.2 to A.12.4.5.4 and B.12.4.5.2 to B.12.4.5.4

Table 10: Incidence of Treatment-Emergent Adverse Events: SAF

Category	Dose-Escalation Cohort				Expansion Cohort
	80 mg† (n = 3)	160 mg (n = 3)	240 mg‡ (n = 3)	Total (n = 9)	160 mg (n = 38)
Treatment-Emergent Adverse Events (TEAEs)	3 (100.0%)	3 (100.0%)	3 (100.0%)	9 (100.0%)	36 (94.7%)
Drug-related TEAEs	2 (66.7%)	3 (100.0%)	2 (66.7%)	7 (77.8%)	24 (63.2%)
TEAEs resulting in death	1 (33.3%)§	0	0	1 (11.1%)	1 (2.6%)††
Serious TEAEs	1 (33.3%)	0	2 (66.7%)	3 (33.3%)	13 (34.2%)
Drug-related serious TEAEs	0	0	0	0	4 (10.5%)
TEAEs leading to permanent discontinuation	1 (33.3%)	0	0	1 (11.1%)	10 (26.3%)
Drug-related TEAEs leading to permanent discontinuation	0	0	0	0	4 (10.5%)
TEAEs leading to temporary discontinuation	0	1 (33.3%)	0	1 (11.1%)	5 (13.2%)
Drug-related TEAEs leading to temporary discontinuation	0	1 (33.3%)	0	1 (11.1%)	2 (5.3%)
Grade 3 or higher TEAEs	1 (33.3%)	2 (66.7%)	3 (100.0%)	6 (66.7%)	24 (63.2%)
Drug-related Grade 3 or higher TEAEs	1 (33.3%)	2 (66.7%)	2 (66.7%)	5 (55.6%)	14 (36.8%)

Number (%) of patients
Safety data from the Single-Dose Period, Multiple-Dose Period and Long-Term Dosing Period were combined for the Dose-Escalation Cohort. Similarly, the Multiple-Dose Period and Long-Term Dosing Period were combined for the Expansion Cohort.
† For patients in the 80-mg group, the dose of MDV3100 was increased to 160 mg during the Long-Term Dosing Period.
‡ All patients in the 240-mg group received MDV3100 at a dose of 160 mg after the Single-Dose Period.
§ One death (due to drowning) was reported and the event was considered unrelated to the study drug.
†† One patient died from disseminated intravascular coagulation that was considered unrelated to the study drug.
Source: Tables A.12.2.1.1, A.12.6.1.1, B.12.6.1.1, A.12.6.1.4.2, B.12.6.1.4.2, Appendices A.13.2.7.3 and B.13.2.7.3

Table 11: Treatment-Emergent Adverse Events in the Dose-Escalation Cohort: SAF

MedDRA v14.1, System Organ Class and Preferred Term	Dose-Escalation Cohort			
	80 mg† (n = 3)	160 mg (n = 3)	240 mg‡ (n = 3)	Total (n = 9)
Overall	**3 (100.0%)**	**3 (100.0%)**	**3 (100.0%)**	**9 (100.0%)**
Blood and lymphatic system disorders	**1 (33.3%)**	**0**	**0**	**1 (11.1%)**
Anaemia	1 (33.3%)	0	0	1 (11.1%)
Eye disorders	**2 (66.7%)**	**0**	**0**	**2 (22.2%)**
Conjunctivitis	2 (66.7%)	0	0	2 (22.2%)
Gastrointestinal disorders	**2 (66.7%)**	**3 (100.0%)**	**1 (33.3%)**	**6 (66.7%)**
Abdominal discomfort	0	1 (33.3%)	0	1 (11.1%)
Constipation	1 (33.3%)§	1 (33.3%)	0	2 (22.2%)
Diarrhoea	0	1 (33.3%)§	1 (33.3%)	2 (22.2%)
Gastritis	0	1 (33.3%)	0	1 (11.1%)
Gingivitis	0	1 (33.3%)	0	1 (11.1%)
Nausea	2 (66.7%)	2 (66.7%)	0	4 (44.4%)
Stomatitis	0	1 (33.3%)	0	1 (11.1%)
General disorders and administration site conditions	**2 (66.7%)**	**3 (100.0%)**	**1 (33.3%)**	**6 (66.7%)**
Death	1 (33.3%)††	0	0	1 (11.1%)
Fatigue	0	1 (33.3%)§	1 (33.3%)§	2 (22.2%)
Malaise	0	2 (66.7%)	0	2 (22.2%)
Oedema peripheral	0	1 (33.3%)	0	1 (11.1%)
Pyrexia	1 (33.3%)§	0	0	1 (11.1%)
Infections and infestations	**1 (33.3%)**	**0**	**0**	**1 (11.1%)**
Nasopharyngitis	1 (33.3%)	0	0	1 (11.1%)
Oral herpes	1 (33.3%)	0	0	1 (11.1%)
Sinusitis	1 (33.3%)	0	0	1 (11.1%)
Urinary tract infection	1 (33.3%)	0	0	1 (11.1%)
Injury, poisoning and procedural complications	**2 (66.7%)**	**0**	**0**	**2 (22.2%)**
Contusion	1 (33.3%)	0	0	1 (11.1%)
Rib fracture	1 (33.3%)	0	0	1 (11.1%)
Investigations	**1 (33.3%)**	**1 (33.3%)**	**1 (33.3%)**	**3 (33.3%)**
Blood alkaline phosphatase increased	1 (33.3%)	0	0	1 (11.1%)
Blood creatinine increased	0	1 (33.3%)	0	1 (11.1%)
Blood phosphorus decreased	0	1 (33.3%)‡‡	0	1 (11.1%)
Blood potassium decreased	0	1 (33.3%)‡‡	0	1 (11.1%)
Blood triglycerides increased	1 (33.3%)	0	0	1 (11.1%)
Neutrophil count decreased	0	0	1 (33.3%)§§	1 (11.1%)
Weight decreased	1 (33.3%)	1 (33.3%)‡‡	0	2 (22.2%)
White blood cell count decreased	0	0	1 (33.3%)‡‡	1 (11.1%)
Metabolism and nutrition disorders	**0**	**1 (33.3%)**	**2 (66.7%)**	**3 (33.3%)**
Decreased appetite	0	1 (33.3%)	2 (66.7%)‡‡	3 (33.3%)
Musculoskeletal and connective tissue disorders	**2 (66.7%)**	**0**	**0**	**2 (22.2%)**
Arthralgia	1 (33.3%)§	0	0	1 (11.1%)
Muscle spasms	1 (33.3%)	0	0	1 (11.1%)

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MedDRA v14.1, System Organ Class and Preferred Term	Dose-Escalation Cohort			
	80 mg† (n = 3)	160 mg (n = 3)	240 mg‡ (n = 3)	Total (n = 9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**1 (33.3%)**	**1 (11.1%)**
Cancer pain	0	0	1 (33.3%)‡‡	1 (11.1%)
Nervous system disorders	**0**	**2 (66.7%)**	**0**	**2 (22.2%)**
Dysgeusia	0	1 (33.3%)	0	1 (11.1%)
Headache	0	1 (33.3%)	0	1 (11.1%)
Hypoaesthesia	0	1 (33.3%)	0	1 (11.1%)
Psychiatric disorders	**1 (33.3%)**	**0**	**0**	**1 (11.1%)**
Insomnia	1 (33.3%)§	0	0	1 (11.1%)
Renal and urinary disorders	**1 (33.3%)**	**2 (66.7%)**	**1 (33.3%)**	**4 (44.4%)**
Glycosuria	0	1 (33.3%)	0	1 (11.1%)
Pollakiuria	0	1 (33.3%)§	0	1 (11.1%)
Proteinuria	0	1 (33.3%)	0	1 (11.1%)
Urinary retention	1 (33.3%)	0	1 (33.3%)	2 (22.2%)
Reproductive system and breast disorders	**2 (66.7%)**	**0**	**0**	**2 (22.2%)**
Breast enlargement	1 (33.3%)	0	0	1 (11.1%)
Breast pain	1 (33.3%)	0	0	1 (11.1%)
Skin and subcutaneous tissue disorders	**0**	**1 (33.3%)**	**2 (66.7%)**	**3 (33.3%)**
Eczema	0	0	1 (33.3%)	1 (11.1%)
Eczema asteatotic	0	0	1 (33.3%)	1 (11.1%)
Urticaria	0	1 (33.3%)	0	1 (11.1%)
Xeroderma	0	0	1 (33.3%)	1 (11.1%)
Vascular disorders	**1 (33.3%)**	**1 (33.3%)**	**1 (33.3%)**	**3 (33.3%)**
Hypertension	1 (33.3%)‡‡	1 (33.3%)‡‡	1 (33.3%)‡‡	3 (33.3%)

Number (%) of patients
Safety data from the Single-Dose Period, Multiple-Dose Period and Long-Term Dosing Period were combined for the Dose-Escalation Cohort.
† For patients in the 80-mg group, the dose of MDV3100 was increased to 160 mg during the Long-Term Dosing Period.
‡ All patients in the 240-mg group received MDV3100 at a dose of 160 mg after the Single-Dose Period.
§ The TEAE occurred during the Single-Dose Period (Appendices A.13.2.5.1.1 and A.13.2.7.1).
†† One death (due to drowning) was reported and the event was considered unrelated to the study drug.
‡‡ Including 1 patient who experienced a Grade 3 TEAE.
§§ Grade 4
Source: Tables A.12.2.1.1, A.12.6.1.2, A.12.6.1.4.1 and Appendix A.13.2.7.3

Table 12: Common (5% or more) Treatment-Emergent Adverse Events by Grade in the Expansion Cohort: SAF

MedDRA v14.1, System Organ Class and Preferred Term	Expansion Cohort (n = 38)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Overall	**2 (5.3%)**	**10 (26.3%)**	**19 (50.0%)**	**4 (10.5%)**	**1 (2.6%)**	**36 (94.7%)**
Blood and lymphatic system disorders	**0**	**1 (2.6%)**	**3 (7.9%)**	**3 (7.9%)**	**1 (2.6%)**	**8 (21.1%)**
Anaemia	0	0	1 (2.6%)	3 (7.9%)	0	4 (10.5%)
Disseminated intravascular coagulation	0	1 (2.6%)	0	1 (2.6%)	1 (2.6%)[†]	3 (7.9%)
Gastrointestinal disorders	**7 (18.4%)**	**12 (31.6%)**	**2 (5.3%)**	**0**	**0**	**21 (55.3%)**
Constipation	3 (7.9%)	7 (18.4%)	0	0	0	10 (26.3%)
Diarrhoea	1 (2.6%)	2 (5.3%)	0	0	0	3 (7.9%)
Faecal incontinence	0	2 (5.3%)	0	0	0	2 (5.3%)
Gastritis	0	2 (5.3%)	0	0	0	2 (5.3%)
Haemorrhoids	1 (2.6%)	1 (2.6%)	0	0	0	2 (5.3%)
Nausea	2 (5.3%)	2 (5.3%)	1 (2.6%)	0	0	5 (13.2%)
Periodontitis	1 (2.6%)	1 (2.6%)	0	0	0	2 (5.3%)
Vomiting	2 (5.3%)	0	1 (2.6%)	0	0	3 (7.9%)
General disorders and administration site conditions	**10 (26.3%)**	**5 (13.2%)**	**3 (7.9%)**	**0**	**0**	**18 (47.4%)**
Fatigue	3 (7.9%)	1 (2.6%)	0	0	0	4 (10.5%)
Gait disturbance	0	2 (5.3%)	1 (2.6%)	0	0	3 (7.9%)
General physical health deterioration	0	0	2 (5.3%)	0	0	2 (5.3%)
Malaise	2 (5.3%)	1 (2.6%)	0	0	0	3 (7.9%)
Oedema	1 (2.6%)	0	1 (2.6%)	0	0	2 (5.3%)
Oedema peripheral	1 (2.6%)	1 (2.6%)	0	0	0	2 (5.3%)
Pyrexia	4 (10.5%)	0	0	0	0	4 (10.5%)
Infections and infestations	**4 (10.5%)**	**6 (15.8%)**	**4 (10.5%)**	**0**	**0**	**14 (36.8%)**
Cellulitis	0	0	2 (5.3%)	0	0	2 (5.3%)
Nasopharyngitis	4 (10.5%)	1 (2.6%)	0	0	0	5 (13.2%)
Pyelonephritis	0	1 (2.6%)	1 (2.6%)	0	0	2 (5.3%)
Urinary tract infection	0	2 (5.3%)	0	0	0	2 (5.3%)
Injury, poisoning and procedural complications	**3 (7.9%)**	**3 (7.9%)**	**0**	**1 (2.6%)**	**0**	**7 (18.4%)**
Contusion	3 (7.9%)	0	0	0	0	3 (7.9%)
Fall	0	1 (2.6%)	0	1 (2.6%)	0	2 (5.3%)
Investigations	**6 (15.8%)**	**13 (34.2%)**	**7 (18.4%)**	**1 (2.6%)**	**0**	**27 (71.1%)**
Blood albumin decreased	0	2 (5.3%)	0	0	0	2 (5.3%)
Blood alkaline phosphatase increased	0	2 (5.3%)	1 (2.6%)	0	0	3 (7.9%)
Blood lactate dehydrogenase increased	2 (5.3%)	0	0	0	0	2 (5.3%)
Blood phosphorus decreased	0	1 (2.6%)	1 (2.6%)	0	0	2 (5.3%)
Blood potassium decreased	0	3 (7.9%)	1 (2.6%)	0	0	4 (10.5%)
Blood pressure increased	0	0	2 (5.3%)	0	0	2 (5.3%)
Electrocardiogram QT prolonged	3 (7.9%)	2 (5.3%)	1 (2.6%)	0	0	6 (15.8%)
Gamma-glutamyltransferase increased	1 (2.6%)	0	0	1 (2.6%)	0	2 (5.3%)
Haemoglobin decreased	1 (2.6%)	1 (2.6%)	0	0	0	2 (5.3%)
Weight decreased	6 (15.8%)	9 (23.7%)	3 (7.9%)	0	0	18 (47.4%)

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MedDRA v14.1, System Organ Class and Preferred Term	Expansion Cohort (n = 38)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Metabolism and nutrition disorders	**1 (2.6%)**	**3 (7.9%)**	**7 (18.4%)**	**0**	**0**	**11 (28.9%)**
Decreased appetite	2 (5.3%)	3 (7.9%)	6 (15.8%)	0	0	11 (28.9%)
Musculoskeletal and connective tissue disorders	**4 (10.5%)**	**6 (15.8%)**	**1 (2.6%)**	**0**	**0**	**11 (28.9%)**
Arthralgia	1 (2.6%)	1 (2.6%)	0	0	0	2 (5.3%)
Muscular weakness	1 (2.6%)	1 (2.6%)	0	0	0	2 (5.3%)
Myalgia	2 (5.3%)	1 (2.6%)	0	0	0	3 (7.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (2.6%)**	**5 (13.2%)**	**7 (18.4%)**	**0**	**0**	**13 (34.2%)**
Cancer pain	0	5 (13.2%)	3 (7.9%)	0	0	8 (21.1%)
Tumour pain	1 (2.6%)	1 (2.6%)	2 (5.3%)	0	0	4 (10.5%)
Nervous system disorders	**8 (21.1%)**	**6 (15.8%)**	**2 (5.3%)**	**0**	**0**	**16 (42.1%)**
Dizziness	2 (5.3%)	1 (2.6%)	0	0	0	3 (7.9%)
Dysgeusia	1 (2.6%)	1 (2.6%)	0	0	0	2 (5.3%)
Hypoaesthesia	2 (5.3%)	1 (2.6%)	0	0	0	3 (7.9%)
Somnolence	4 (10.5%)	1 (2.6%)	0	0	0	5 (13.2%)
Psychiatric disorders	**5 (13.2%)**	**1 (2.6%)**	**0**	**0**	**0**	**6 (15.8%)**
Delirium	2 (5.3%)	1 (2.6%)	0	0	0	3 (7.9%)
Insomnia	2 (5.3%)	0	0	0	0	2 (5.3%)
Renal and urinary disorders	**2 (5.3%)**	**6 (15.8%)**	**2 (5.3%)**	**1 (2.6%)**	**0**	**11 (28.9%)**
Bladder tamponade	0	0	2 (5.3%)	0	0	2 (5.3%)
Haematuria	2 (5.3%)	2 (5.3%)	1 (2.6%)	0	0	5 (13.2%)
Hydronephrosis	0	4 (10.5%)	0	0	0	4 (10.5%)
Urinary retention	0	3 (7.9%)	0	0	0	3 (7.9%)
Reproductive system and breast disorders	**0**	**0**	**2 (5.3%)**	**0**	**0**	**2 (5.3%)**
Prostatitis	0	0	2 (5.3%)	0	0	2 (5.3%)
Respiratory, thoracic and mediastinal disorders	**2 (5.3%)**	**1 (2.6%)**	**0**	**1 (2.6%)**	**0**	**4 (10.5%)**
Pleural effusion	2 (5.3%)	0	0	0	0	2 (5.3%)
Skin and subcutaneous tissue disorders	**5 (13.2%)**	**3 (7.9%)**	**0**	**0**	**0**	**8 (21.1%)**
Dry skin	1 (2.6%)	1 (2.6%)	0	0	0	2 (5.3%)
Rash	4 (10.5%)	1 (2.6%)	0	0	0	5 (13.2%)
Vascular disorders	**1 (2.6%)**	**2 (5.3%)**	**5 (13.2%)**	**1 (2.6%)**	**0**	**9 (23.7%)**
Hot flush	3 (7.9%)	0	0	0	0	3 (7.9%)
Hypertension	0	2 (5.3%)	5 (13.2%)	0	0	7 (18.4%)

Number (%) of patients
Safety data from the Multiple-Dose Period and Long-Term Dosing Period were combined for the Expansion Cohort.
† One patient died from disseminated intravascular coagulation that was considered unrelated to the study drug.
Source: Table B.12.6.1.4.1 and Appendix B.13.2.7.3

Table 13: Drug-Related Treatment-Emergent Adverse Events: SAF

MedDRA v14.1, System Organ Class and Preferred Term	Dose-Escalation Cohort				Expansion Cohort
	80 mg[†] (n = 3)	160 mg (n = 3)	240 mg[‡] (n = 3)	Total (n = 9)	160 mg (n = 38)
Overall	**2 (66.7%)**	**3 (100.0%)**	**2 (66.7%)**	**7 (77.8%)**	**24 (63.2%)**
Blood and lymphatic system disorders	**0**	**0**	**0**	**0**	**2 (5.3%)**
Anaemia	0	0	0	0	2 (5.3%)
Disseminated intravascular coagulation	0	0	0	0	1 (2.6%)
Cardiac disorders	**0**	**0**	**0**	**0**	**2 (5.3%)**
Arrhythmia supraventricular	0	0	0	0	1 (2.6%)
Ventricular extrasystoles	0	0	0	0	1 (2.6%)
Eye disorders	**1 (33.3%)**	**0**	**0**	**1 (11.1%)**	**1 (2.6%)**
Conjunctivitis	1 (33.3%)	0	0	1 (11.1%)	0
Glaucoma	0	0	0	0	1 (2.6%)
Gastrointestinal disorders	**1 (33.3%)**	**3 (100.0%)**	**1 (33.3%)**	**5 (55.6%)**	**14 (36.8%)**
Abdominal discomfort	0	1 (33.3%)	0	1 (11.1%)	1 (2.6%)
Abdominal pain upper	0	0	0	0	1 (2.6%)
Constipation	0	1 (33.3%)	0	1 (11.1%)	6 (15.8%)
Diarrhoea	0	1 (33.3%)[§]	1 (33.3%)	2 (22.2%)	1 (2.6%)
Dry mouth	0	0	0	0	1 (2.6%)
Faecal incontinence	0	0	0	0	1 (2.6%)
Gastritis	0	1 (33.3%)	0	1 (11.1%)	2 (5.3%)
Haemorrhoids	0	0	0	0	1 (2.6%)
Nausea	1 (33.3%)	0	0	1 (11.1%)	2 (5.3%)
Periodontal disease	0	0	0	0	1 (2.6%)
Salivary hypersecretion	0	0	0	0	1 (2.6%)
Stomatitis	0	1 (33.3%)[§]	0	1 (11.1%)	0
Vomiting	0	0	0	0	2 (5.3%)
General disorders and administration site conditions	**1 (33.3%)**	**1 (33.3%)**	**1 (33.3%)**	**3 (33.3%)**	**9 (23.7%)**
Chest pain	0	0	0	0	1 (2.6%)
Fatigue	0	1 (33.3%)[§]	1 (33.3%)[§]	2 (22.2%)	4 (10.5%)
Gait disturbance	0	0	0	0	2 (5.3%)
Malaise	0	0	0	0	2 (5.3%)
Oedema	0	0	0	0	1 (2.6%)
Pyrexia	1 (33.3%)[§]	0	0	1 (11.1%)	0
Infections and infestations	**0**	**0**	**0**	**0**	**2 (5.3%)**
Cellulitis	0	0	0	0	1 (2.6%)
Lung infection	0	0	0	0	1 (2.6%)
Injury, poisoning and procedural complications	**0**	**0**	**0**	**0**	**2 (5.3%)**
Fall	0	0	0	0	2 (5.3%)

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MedDRA v14.1, System Organ Class and Preferred Term	Dose-Escalation Cohort				Expansion Cohort
	80 mg† (n = 3)	160 mg (n = 3)	240 mg‡ (n = 3)	Total (n = 9)	160 mg (n = 38)
Investigations	**0**	**1 (33.3%)**	**0**	**1 (11.1%)**	**13 (34.2%)**
Blood alkaline phosphatase increased	0	0	0	0	1 (2.6%)
Blood creatinine increased	0	1 (33.3%)	0	1 (11.1%)	0
Blood phosphorus decreased	0	1 (33.3%)††	0	1 (11.1%)	1 (2.6%)
Blood potassium decreased	0	1 (33.3%)††	0	1 (11.1%)	0
Blood pressure increased	0	0	0	0	1 (2.6%)
Blood triglycerides increased	0	0	0	0	1 (2.6%)
Electrocardiogram QT prolonged	0	0	0	0	5 (13.2%)
Gamma-glutamyltransferase increased	0	0	0	0	1 (2.6%)
Protein urine present	0	0	0	0	1 (2.6%)
Weight decreased	0	1 (33.3%)††	0	1 (11.1%)	5 (13.2%)
Weight increased	0	0	0	0	1 (2.6%)
Metabolism and nutrition disorders	**0**	**1 (33.3%)**	**1 (33.3%)**	**2 (22.2%)**	**5 (13.2%)**
Decreased appetite	0	1 (33.3%)	1 (33.3%)††	2 (22.2%)	4 (10.5%)
Dehydration	0	0	0	0	1 (2.6%)
Musculoskeletal and connective tissue disorders	**0**	**0**	**0**	**0**	**2 (5.3%)**
Arthralgia	0	0	0	0	1 (2.6%)
Back pain	0	0	0	0	1 (2.6%)
Musculoskeletal pain	0	0	0	0	1 (2.6%)
Musculoskeletal stiffness	0	0	0	0	1 (2.6%)
Periarthritis	0	0	0	0	1 (2.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**0**	**0**	**2 (5.3%)**
Cancer pain	0	0	0	0	1 (2.6%)
Tumour pain	0	0	0	0	1 (2.6%)
Nervous system disorders	**0**	**2 (66.7%)**	**0**	**2 (22.2%)**	**8 (21.1%)**
Dizziness	0	0	0	0	3 (7.9%)
Dysgeusia	0	1 (33.3%)	0	1 (11.1%)	2 (5.3%)
Headache	0	1 (33.3%)	0	1 (11.1%)	0
Hypoaesthesia	0	1 (33.3%)	0	1 (11.1%)	2 (5.3%)
Intention tremor	0	0	0	0	1 (2.6%)
Somnolence	0	0	0	0	1 (2.6%)
Renal and urinary disorders	**0**	**1 (33.3%)**	**0**	**1 (11.1%)**	**2 (5.3%)**
Glycosuria	0	1 (33.3%)	0	1 (11.1%)	0
Haematuria	0	0	0	0	1 (2.6%)
Proteinuria	0	1 (33.3%)	0	1 (11.1%)	0
Renal failure acute	0	0	0	0	1 (2.6%)
Urinary retention	0	0	0	0	1 (2.6%)
Reproductive system and breast disorders	**1 (33.3%)**	**0**	**0**	**1 (11.1%)**	**0**
Breast enlargement	1 (33.3%)	0	0	1 (11.1%)	0

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MedDRA v14.1, System Organ Class and Preferred Term	Dose-Escalation Cohort				Expansion Cohort
	80 mg† (n = 3)	160 mg (n = 3)	240 mg‡ (n = 3)	Total (n = 9)	160 mg (n = 38)
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**0**	**0**	**1 (2.6%)**
Acute respiratory distress syndrome	0	0	0	0	1 (2.6%)
Pulmonary oedema	0	0	0	0	1 (2.6%)
Skin and subcutaneous tissue disorders	**0**	**0**	**0**	**0**	**4 (10.5%)**
Dry skin	0	0	0	0	2 (5.3%)
Pruritus	0	0	0	0	1 (2.6%)
Rash	0	0	0	0	1 (2.6%)
Skin ulcer	0	0	0	0	1 (2.6%)
Vascular disorders	**1 (33.3%)**	**1 (33.3%)**	**1 (33.3%)**	**3 (33.3%)**	**7 (18.4%)**
Hot flush	0	0	0	0	2 (5.3%)
Hypertension	1 (33.3%)††	1 (33.3%)††	1 (33.3%)††	3 (33.3%)	5 (13.2%)
Hypotension	0	0	0	0	1 (2.6%)

Number (%) of patients
Safety data from the Single-Dose Period, Multiple-Dose Period and Long-Term Dosing Period were combined for the Dose-Escalation Cohort. Similarly, the Multiple-Dose Period and Long-Term Dosing Period were combined for the Expansion Cohort.
† For patients in the 80-mg group, the dose of MDV3100 was increased to 160 mg during the Long-Term Dosing Period.
‡ All patients in the 240-mg group received MDV3100 at a dose of 160 mg after the Single-Dose Period.
§ The TEAE occurred during the Single-Dose Period (Appendices A.13.2.5.1.1 and A.13.2.7.1).
†† Grade 3.
Source: Tables A.12.2.1.1, A.12.6.1.3, A.12.6.1.5.1 and B.12.6.1.3

Table 14: Serious Treatment-Emergent Adverse Events: SAF

MedDRA v14.1, System Organ Class and Preferred Term	Dose-Escalation Cohort				Expansion Cohort
	80 mg† (n = 3)	160 mg (n = 3)	240 mg‡ (n = 3)	Total (n = 9)	160 mg (n = 38)
Overall	**1 (33.3%)**	**0**	**2 (66.7%)**	**3 (33.3%)**	**13 (34.2%)**
Blood and lymphatic system disorders	**0**	**0**	**0**	**0**	**3 (7.9%)**
Anaemia	0	0	0	0	2 (5.3%)
Disseminated intravascular coagulation	0	0	0	0	2 (5.3%)
Leukopenia	0	0	0	0	1 (2.6%)
Gastrointestinal disorders	**0**	**0**	**0**	**0**	**1 (2.6%)**
Vomiting	0	0	0	0	1 (2.6%)
General disorders and administration site conditions	**1 (33.3%)**	**0**	**0**	**1 (11.1%)**	**3 (7.9%)**
Death	1 (33.3%)§	0	0	1 (11.1%)	0
Gait disturbance	0	0	0	0	1 (2.6%)
General physical health deterioration	0	0	0	0	2 (5.3%)
Infections and infestations	**0**	**0**	**0**	**0**	**3 (7.9%)**
Cellulitis	0	0	0	0	2 (5.3%)
Pyelonephritis acute	0	0	0	0	1 (2.6%)

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MedDRA v14.1, System Organ Class and Preferred Term	Dose-Escalation Cohort				Expansion Cohort
	80 mg† (n = 3)	160 mg (n = 3)	240 mg‡ (n = 3)	Total (n = 9)	160 mg (n = 38)
Injury, poisoning and procedural complications	**0**	**0**	**0**	**0**	**1 (2.6%)**
Fall	0	0	0	0	1 (2.6%)
Traumatic haemorrhage	0	0	0	0	1 (2.6%)
Investigations	**0**	**0**	**1 (33.3%)**	**1 (11.1%)**	**0**
Neutrophil count decreased	0	0	1 (33.3%)	1 (11.1%)	0
White blood cell count decreased	0	0	1 (33.3%)	1 (11.1%)	0
Metabolism and nutrition disorders	**0**	**0**	**0**	**0**	**1 (2.6%)**
Dehydration	0	0	0	0	1 (2.6%)
Musculoskeletal and connective tissue disorders	**0**	**0**	**0**	**0**	**2 (5.3%)**
Bone pain	0	0	0	0	1 (2.6%)
Spinal osteoarthritis	0	0	0	0	1 (2.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**1 (33.3%)**	**1 (11.1%)**	**6 (15.8%)**
Brain cancer metastatic	0	0	0	0	1 (2.6%)
Cancer pain	0	0	1 (33.3%)	1 (11.1%)	2 (5.3%)
Tumour haemorrhage	0	0	0	0	1 (2.6%)
Tumour pain	0	0	0	0	2 (5.3%)
Nervous system disorders	**0**	**0**	**0**	**0**	**3 (7.9%)**
Lacunar infarction	0	0	0	0	1 (2.6%)
Monoplegia	0	0	0	0	1 (2.6%)
Thalamus haemorrhage	0	0	0	0	1 (2.6%)
Renal and urinary disorders	**0**	**0**	**0**	**0**	**3 (7.9%)**
Bladder tamponade	0	0	0	0	2 (5.3%)
Haematuria	0	0	0	0	1 (2.6%)
Renal failure acute	0	0	0	0	1 (2.6%)
Urinary retention	0	0	0	0	1 (2.6%)
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**0**	**0**	**1 (2.6%)**
Acute respiratory distress syndrome	0	0	0	0	1 (2.6%)
Pulmonary oedema	0	0	0	0	1 (2.6%)
Vascular disorders	**0**	**0**	**0**	**0**	**1 (2.6%)**
Hypotension	0	0	0	0	1 (2.6%)

Number (%) of patients
Safety data from the Single-Dose Period, Multiple-Dose Period and Long-Term Dosing Period were combined for the Dose-Escalation Cohort. Similarly, the Multiple-Dose Period and Long-Term Dosing Period were combined for the Expansion Cohort.
† For patients in the 80-mg group, the dose of MDV3100 was increased to 160 mg during the Long-Term Dosing Period.
‡ All patients in the 240-mg group received MDV3100 at a dose of 160 mg after the Single-Dose Period.
§ One death (due to drowning) was reported and the event was considered unrelated to the study drug.
Source: Tables A.12.2.1.1, A.12.6.1.7, B.12.6.1.7 and Appendix A.13.2.7.3

Table 15: Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of the Study Drug: SAF

MedDRA v14.1, System Organ Class and Preferred Term	Dose-Escalation Cohort†‡ Any Dose Group (n = 9)	Expansion Cohort 160 mg (n = 38)
Overall	**1 (11.1%)**	**10 (26.3%)**
Blood and lymphatic system disorders	**0**	**1 (2.6%)**
Disseminated intravascular coagulation	0	1 (2.6%)
General disorders and administration site conditions	**1 (11.1%)**	**3 (7.9%)**
Death	1 (11.1%)§	0
Gait disturbance	0	1 (2.6%)
General physical health deterioration	0	2 (5.3%)
Injury, poisoning and procedural complications	**0**	**1 (2.6%)**
Fall	0	1 (2.6%)
Traumatic haemorrhage	0	1 (2.6%)
Investigations	**0**	**1 (2.6%)**
Weight decreased	0	1 (2.6%)
Metabolism and nutrition disorders	**0**	**2 (5.3%)**
Decreased appetite	0	1 (2.6%)
Dehydration	0	1 (2.6%)
Musculoskeletal and connective tissue disorders	**0**	**1 (2.6%)**
Bone pain	0	1 (2.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**2 (5.3%)**
Cancer pain	0	2 (5.3%)
Nervous system disorders	**0**	**1 (2.6%)**
Dizziness	0	1 (2.6%)
Renal and urinary disorders	**0**	**1 (2.6%)**
Bladder tamponade	0	1 (2.6%)
Vascular disorders	**0**	**1 (2.6%)**
Hypotension	0	1 (2.6%)

Number (%) of patients
Safety data from the Single-Dose Period, Multiple-Dose Period and Long-Term Dosing Period were combined for the Dose-Escalation Cohort. Similarly, the Multiple-Dose Period and Long-Term Dosing Period were combined for the Expansion Cohort.
† For patients in the 80-mg group, the dose of MDV3100 was increased to 160 mg during the Long-Term Dosing Period.
‡ All patients in the 240-mg group received MDV3100 at a dose of 160 mg after the Single-Dose Period.
§ One death (due to drowning) was reported and the event was considered unrelated to the study drug.
Source: Tables A.12.2.1.1, A.12.6.1.9.1, B.12.6.1.9.1 and Appendix A.13.2.7.3