Sponsor

Novartis

Generic Drug Name

Vadimezan (ASA404)

Therapeutic Area of Trial

Adult Patients with advanced cancer with impaired renal function and with normal renal function.

Approved Indication

Investigational

Study Number

CASA404A2109

Title

A multi-center, open-label, dose-escalation study to assess the pharmacokinetics of intravenous ASA404 in adult advanced cancer patients with impaired renal function and with normal renal function

Phase of Development

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Study Start/End Dates

01-Mar-2010 to 30-Nov-2010

Study Design/Methodology

This was a multi-center, open-label, dose-escalation study to assess the pharmacokinetics (PK) and safety of intravenous ASA404 in adult advanced cancer patients with varying degrees of impaired renal function or normal renal function. Study patients were categorized into three treatment groups: normal renal function group, mild renal impairment group and moderate renal impairment group, based upon their pre-dose creatinine clearance levels.

The study consisted of two phases, a Core phase and an Extension phase. During the Core phase, study patients were assigned to 4 Cycles of study treatment. Cycles 1 and 2 consisted of ASA404 monotherapy with 900 mg/m², 1200 mg/m² or 1800 mg/m². In Cycle 3 and Cycle 4, ASA404 was co-administered with chemotherapy (docetaxel or paclitaxel + carboplatin). The Extension phase allowed patients to continue therapy.

Due to premature study termination, the pharmacokinetic parameters (primary objectives) were not calculated and no statistical analyses are reported. Hence an abbreviated clinical study report (CSR) was prepared presenting results on safety variables.

Centers

USA (3), New Zealand (1), France (1)

Publication

Not applicable

Objectives

Primary objective(s)

Core phase only: To evaluate the pharmacokinetics of a single intravenous dose of ASA404 1200 mg/m² and 1800 mg/m² monotherapy in adult advanced cancer patients with various degrees of impaired renal function as compared to matching patients with normal renal function.

Extension phase only: To assess the safety and tolerability of ASA404 1200 or 1800 mg/m² in combination with chemotherapy (docetaxel or paclitaxel + carboplatin) in adult advanced cancer patients with various degrees of impaired renal function or normal renal function.

Secondary objective(s)

Core phase only

- To evaluate the pharmacokinetics of a single intravenous dose of ASA404 1200 mg/m² + chemotherapy (docetaxel or paclitaxel + carboplatin) and ASA404 1800 mg/m² + chemotherapy (docetaxel or paclitaxel + carboplatin) in adult advanced cancer patients with various degrees of impaired renal function compared to matching patients with normal renal function.
- To assess the safety and tolerability of ASA404 in adult advanced cancer patients with various degrees of impaired renal function as compared to matching patients with normal renal function.

Test Product (s), Dose(s), and Mode(s) of Administration

In the Core phase, ASA404 was administered at a starting dose of 1200 mg/m² monotherapy as a 50-mL iv infusion over a period of 20 minutes on Day 1 of Cycle 1, with subsequent dose escalation to 1800 mg/m² in Cycle 2. Similarly, following the administration of docetaxel or paclitaxel and carboplatin, ASA404 was administered at a dose of 1200 mg/m² on Day 1 of Cycle 3, with subsequent dose escalation to 1800 mg/m² in Cycle 4. Eligible patients continued the study treatment in the Extension phase.

Reference Product(s), Dose(s), and Mode(s) of Administration

Not applicable

Criteria for Evaluation

Efficacy

Not applicable

Safety

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies, and regular monitoring of hematology, blood chemistry, electrocardiogram (ECG), urinalysis, and regular assessment of vital signs, physical condition and body weight. The assessment of safety was based mainly on the frequency of adverse events and on the number of abnormal laboratory values that were new or worsening based upon the common terminology criteria for adverse events (CTCAE v3.0).

Bioanalytics

Plasma concentrations of ASA404 were measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) of approximately 100 ng/mL. However, due to premature study termination, the PK parameters were not calculated.

Statistical Methods

The primary variables were non-compartmental PK parameters (AUC_{last}, AUC_{∞}, λ_z, $t_{1/2}$, T_{max}, C_{max}, C_L, V_z) characterizing the dispositions of ASA404. Due to premature study termination, no individual PK parameters were calculated and no analyses were reported.

All adverse events recorded during the study were listed by renal function group. The incidence (number and percentage) of all treatment emergent adverse events (TEAEs) was tabulated by system organ class (SOC), preferred term and renal function group. All adverse events recorded during the study were listed by renal function group. All laboratory values were converted into SI units and classified by severity grades using CTCAE version 3.0. Individual data listings by renal function group were provided for all vital sign, ECG and laboratory parameters with notable and out-of-range values flagged.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Patients having histologically-proven solid tumors, who were either refractory to standard chemotherapy and for whom chemotherapy with an investigational agent in combination with docetaxel, or paclitaxel + carboplatin was appropriate
2. Age ≥ 18 years old
3. WHO Performance Status (PS) of 0-2
4. Written informed consent obtained prior to any screening procedures
5. A minimum of 4 weeks were to have elapsed since the last treatment with other cancer therapies, (e.g., endocrine therapy, immunotherapy, chemotherapy, etc.), and 6 weeks for nitrosoureas and mitomycin C

6. Females of child-bearing potential were to have negative serum pregnancy test at screening (confirmation of negative urine pregnancy test within 72 hours prior to initial dosing of study drug)
7. Body Mass Index (BMI) was to be within the range of 18 and 30
8. Minimum weight of 50 kg
9. Laboratory values within the range, as defined below, within 2 weeks of starting study drug:
   - Creatinine clearance according to Cockcroft-Gault formula
   - Urinalysis (no evidence of proteinuria [≥ +2 or >100 mg/dL on urine dipstick], hematuria [≥ +1 blood on urine dipstick] for 'normal' impairment cohort patients)
   - Absolute neutrophil count (ANC) >2.0 x 10^9/L
   - Platelets ≥ 100 x 10^9/L
   - Hemoglobin ≥ 10 g/dL
   - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 x ULN. If liver function abnormalities were due to liver metastases, then AST and ALT may be ≤ 5 x ULN
   - Prothrombin Time (PT) ≤ 1.5 x ULN
   - Partial Thromboplastin Time (PTT) ≤ 1.5 x ULN
   - Potassium, calcium, magnesium and phosphorus values within the normal range. Patients with corrected electrolyte values were eligible.
   - Serum total bilirubin ≤ 1.5 x ULN (≤ 25 micromol/L)

Exclusion Criteria

1. Patients having central nervous system (CNS) metastases. Patients having any clinical signs of CNS metastases were to have a CT or MRI of the brain performed to rule out CNS metastases in order to be eligible for study participation. Patients who had brain metastases surgically removed or irradiated with no active residual disease confirmed by imaging were allowed.
2. Patients with leptomeningeal disease metastases were not allowed on study
3. Radiotherapy ≤ 4 weeks prior to starting study drug. Patients were to have recovered from all acute radiotherapy-related toxicities
4. Major surgery ≤ 4 weeks prior to starting study drug. Major surgery was defined as any invasive operative procedure in which extensive resection was performed (e.g., a body cavity was entered, organs were removed, mesenchymal barrier was opened, an extensive orthopedic procedure was involved, or normal anatomy was significantly altered). Patients were to have recovered from all acute surgery-related complications
5. Minor surgery ≤ 2 weeks prior to starting study drug. Minor surgery was defined as any invasive operative procedure in which only skin or mucous membranes and connective tissue were resected (e.g., vascular cutdown for catheter placement, implanting pumps in subcutaneous tissue, biopsies, placement of probes or catheters requiring the entry into a body cavity, tooth extractions, and gingival grafts). Insertion of a vascular access device was allowed. Patients were to have recovered from all acute surgery-related complications

5. Concurrent use of other investigational agents and patients who had received investigational agents within 4 weeks (or longer if required by local regulation) prior to starting study drug
6. Concurrent use of any homeopathic or naturopathic medicines
7. Administration of CYP1A2 and CYP3A4/5 enzyme inducing or inhibiting drugs within 14 days (or 5 half-lives, if longer) prior to starting study drug
8. Concurrent use of all inducers or inhibitors of UGT1A9 and UGT2B7 (uridine diphosphate glycosyltransferase) within 7 days prior to starting study drug
9. Prior exposure to Vascular Disrupting Agents (VDAs), e.g. fosbretabulin, crinobulin. VDAs are a class of anti-cancer agents targeting existing tumor vasculature and are distinct from anti-angiogenesis agents which target neovascularization of tumors. Prior use of anti-angiogenesis agents, such as VEGF/VEGF receptor inhibitors, was allowed, e.g. sorafenib, bevacizumab, etc.
10. Patients with systolic BP <100 mmHg or >160 mmHg and/or diastolic BP <60 mmHg or >90 mmHg
11. Patients with any one of the following:
    - Long QT syndrome
    - Family history of unexplained sudden death
    - Screening 12-lead ECG QTcF of > 450 using the Fridericia [QTcF] measurement determined by the central ECG evaluation report
    - Congestive heart failure (NY Heart Association class III or IV)
    - Myocardial infarction within 12 months of starting study drug
    - Unstable or poorly controlled angina pectoris, including Prinzmetal variant angina pectoris
    - History of labile hypertension or poor compliance with antihypertensive regimen
    - History of a sustained ventricular tachycardia
    - History of ventricular fibrillation or torsade de pointes (TdP)
    - History of atrial tachyarrhythmia, (e.g., atrial fibrillation, atrial flutter, multifocal atrial tachycardia, supraventricular tachycardia), if not rate controlled
    - Right bundle branch block (RBBB), complete left bundle branch block (LBBB), bifascicular block (right bundle branch block with either left anterior hemiblock or left posterior hemiblock)
    - Bradycardia defined as heart rate <50 beats per minute
    - Any clinically significant ST segment and/or T wave abnormalities
    - Use of a cardiac pacemaker or defibrillator
13. Concomitant use of drugs with a known risk of prolonging QT interval or causing torsade de pointes. Patients who were taking these drugs at the time of screening were allowed to be enrolled only if the patient was able to discontinue these medications within 14 days (or 5 half-lives, if longer) prior to starting study drug and able to switch to a protocol-permitted medication to treat their medical condition for the duration of their participation in the study.
14. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laborato-

ry test (>5 mIU/mL)

15. Concurrent severe and/or uncontrolled medical disease (e.g., uncontrolled diabetes, chronic liver disease, confirmed diagnosis of HIV infection, or active uncontrolled infection), that could cause unacceptable safety risks or compromise compliance with protocol
16. Known history of seizures requiring anti-convulsant therapy
17. Significant neurologic or psychiatric disorder which could compromise participation in the study
18. Donation or loss of 400 mL of blood within 4 weeks prior to starting study drug
19. History of gastrointestinal bleeding in the preceding 3 weeks of starting study drug
20. Women of child bearing potential or sexually active males, unwilling or unable to use the required highly effective method(s) of contraception for both sexes while receiving treatment and for at least 6 months after the discontinuation of study treatment. Adequate forms of contraception include IUD, oral or depot contraceptive or the barrier method plus spermicide. *Note: if a patient was to be treated with paclitaxel, please see Exclusion Criteria #26.
21. Consumption of grapefruit, grapefruit juice, star fruit, star fruit juice or caffeinated beverages within 48 hours of starting study drug. (Consumption was allowed during the Extension phase).
22. Patients receiving full-dose therapeutic oral or parenteral anticoagulation were ineligible. Patients receiving thrombolytic therapy within 10 days of starting were also ineligible. Patients may receive prophylactic anticoagulation therapy for port clot prophylaxis.
23. Patients unwilling or unable to comply with the protocol

If a patient was to be treated with paclitaxel:

24. Known allergy or hypersensitivity to platinum-containing drugs, taxanes, other drugs formulated in Cremophor EL (polyoxyethylated castor oil) or any known excipients of these drugs
25. Peripheral sensory neuropathy with functional impairment (Common Terminology Criteria for Adverse Events (CTCAE) v3.0 Grade 2 neuropathy, regardless of causality)
26. Oral, implantable, or injectable contraceptives might be affected by cytochrome P450 interactions while taking paclitaxel and therefore were not considered effective contraceptive methods for this study when used as a single agent. Therefore, it was highly recommended that a concomitant barrier method be used with oral, implantable, or injectable contraceptives. Patients taking oral, implantable, or injectable contraceptives who were not willing or otherwise unable to use a concomitant barrier method were excluded.

If a patient was to be treated with docetaxel:

27. Known allergy or hypersensitivity to drugs formulated with polysorbate 80 or any known excipients of these drugs

Number of Subjects

Patient disposition by renal function group (FAS)

Disposition	Normal Control N=7 n (%)	Mild Impairment N=5 n (%)	All patients N=12 n (%)
Enrolled	7 (100.0)	5 (100.0)	12 (100.0)
Completed*	2 (28.6)	2 (40.0)	4 (33.3)
Disease progression	2 (28.6)	1 (20.0)	3 (25.0)
Treatment duration completed as per protocol	0	1 (20.0)	1 (8.3)
Discontinued	5 (71.4)	3 (60.0)	8 (66.7)
Adverse Event(s)	2 (28.6)	0	2 (16.7)
Abnormal laboratory value(s)	0	0	0
Abnormal test procedure result(s)	0	0	0
Patient withdrew consent	1 (14.3)	1 (20.0)	2 (16.7)
Lost to follow-up	0	0	0
Administrative problems	2 (28.6)	2 (40.0)	4 (33.3)
Protocol deviation	0	0	0
Entered Extension phase	0	1 (20.0)	1 (8.3)

*A patient was considered to have completed the study if the primary reason for end of treatment in the CRF was ‘Death’, ‘Disease progression’ or ‘Treatment duration completed as per protocol’.

Note: Table includes all patients at the time of analysis, regardless of which phase they ended treatment in.

Demographic and Background Characteristics

Demographics and other baseline characteristics, by renal function group (FAS)

Demographic Variables	Normal Control (N=7)	Mild Impairment (N=5)	All patients (N=12)
Age (years)			
Mean (SD)	60.9 (7.08)	60.6 (8.91)	60.8 (7.5)
Median (Min-max)	63 (47-67)	64 (47-70)	63.5 (47-70)
Sex, n (%)			
Male	5 (71.4)	4 (80.0)	9 (75.0)
Female	2 (28.6)	1 (20.0)	3 (25.0)
Race, n (%)			
Caucasian	5 (71.4)	5 (100.0)	10 (83.3)
Asian	2 (28.6)	0	2 (16.7)
Ethnicity, n (%)			
Chinese	1 (14.3)	0	1 (8.3)
Indian (Indian subcontinent)	1 (14.3)	0	1 (8.3)

Other	5 (71.4)	5 (100.0)	10 (83.3)
Weight (kg)			
Mean (SD)	66 (12.825)	74.7 (9.211)	69.63 (11.859)
Median (Min-max)	75.2 (51.9-78.1)	74.6 (65.3-86)	74.9 (51.9-86)
Height (cm)			
Mean (SD)	165.3 (9.18)	176.2 (6.61)	169.8 (9.67)
Median (Min-max)	161 (155-178)	175 (170-187)	171.5 (155-187)
BMI (kg/m^2)			
Mean (SD)	23.97 (3.129)	24.02 (2.35)	23.99 (2.711)
Median (Min-max)	24.1 (20.5-29)	23.8 (21.3-27.6)	23.95 (20.5-29)
BSA (m^2)			
Mean (SD)	1.71 (0.204)	1.92 (0.13)	1.8 (0.2)
Median (Min-max)	1.8 (1.5-1.9)	1.9 (1.8-2.1)	1.85 (1.5-2.1)

Note: Baseline was defined as the last available assessment or value before the start of the first treatment in Core phase

Primary Objective Result(s)

Due to premature study termination, the PK parameters (primary objectives) were not calculated and no statistical analyses are reported. The abbreviated report presented only the safety data from the study.

Secondary Objective Result(s)

Safety results are tabulated below.

Safety results

All adverse events, regardless of study drug relationship, by primary system organ class and renal function (Safety set)

Primary system organ class	Normal Control (N=7) n (%)	Mild Impairment (N=5) n (%)	Total (N=12) n (%)
Any primary system organ class	7 (100.0)	4 (80.0)	11 (91.7)
Blood and lymphatic system disorders	2 (28.6)	1 (20.0)	3 (25.0)
Cardiac disorders	1 (14.3)	0	1 (8.3)
Eye disorders	4 (57.1)	2 (40.0)	6 (50.0)
Gastrointestinal disorders	6 (85.7)	3 (60.0)	9 (75.0)
General disorders and administration site conditions	4 (57.1)	4 (80.0)	8 (66.7)

Immune system disorders	0	1 (20.0)	1 (8.3)
Infections and infestations	2 (28.6)	1 (20.0)	3 (25.0)
Injury, poisoning and procedural complications	2 (28.6)	1 (20.0)	3 (25.0)
Investigations	2 (28.6)	1 (20.0)	3 (25.0)
Metabolism and nutrition disorders	1 (14.3)	0	1 (8.3)
Musculoskeletal and connective tissue disorders	4 (57.1)	2 (40.0)	6 (50.0)
Nervous system disorders	3 (42.9)	1 (20.0)	4 (33.3)
Psychiatric disorders	0	2 (40.0)	2 (16.7)
Renal and urinary disorders	2 (28.6)	0	2 (16.7)
Respiratory, thoracic and mediastinal disorders	3 (42.9)	1 (20.0)	4 (33.3)
Skin and subcutaneous tissue disorders	3 (42.9)	3 (60.0)	6 (50.0)
Vascular disorders	1 (14.3)	1 (20.0)	2 (16.7)

- Primary system organ classes are presented alphabetically
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

Most Frequently Reported AEs Overall by Preferred Term n (%)

Preferred term	Normal Control (N=7) n (%)	Mild Impairment (N=5) n (%)	Total (N=12) n (%)
Fatigue	2 (28.6)	3 (60.0)	5 (41.7)
Nausea	2 (28.6)	3 (60.0)	5 (41.7)
Visual impairment	3 (42.9)	2 (40.0)	5 (41.7)
Diarrhea	3 (42.9)	1 (20.0)	4 (33.3)
Headache	3 (42.9)	1 (20.0)	4 (33.3)
Infusion related reaction	2 (28.6)	1 (20.0)	3 (25.0)
Pain of skin	2 (28.6)	1 (20.0)	3 (25.0)

- Preferred terms are sorted by descending order of frequencies, as reported in the Total column
- A patient with multiple occurrences of an AE under one cycle or under the Total column is counted only once in the AE category for that cycle or for the Total column.

Serious Adverse Events and Deaths

Deaths, other serious or clinically significant AEs and discontinuations because of AEs

Patient A2109-0505-00003 from the normal renal function group died due to disease progression within the 28 day follow-up period.

There were 8 SAEs reported in 5 patients, 4 patients from the normal renal function group and 1 patient from the mild renal impairment group. Of the 8 SAEs, 7 were not suspected to be study drug (ASA404) related by the Investigator.

Overall, 2 patients, both in the normal renal function group discontinued the study treatment due to SAEs: one patient had grade 3 cerebrovascular accident (reported as not suspected to be study drug related by the Investigator) and one patient had grade 3 hypertension (reported as suspected to be study drug related by the Investigator). The event of grade 3 hypertension was considered to be a DLT.

Thrombocytopenia (grade 1) was the only AE that led to dose interruption in 1 patient from the mild renal impairment group.

Other Relevant Findings

Not applicable

Date of Clinical Trial Report

24-Jan-2012 (content final)

Date Inclusion on Novartis Clinical Trial Results Database

27-Feb-2012

Date of Latest Update