Sponsor

Novartis

Generic Drug Name

Vadimezan (ASA404)

Therapeutic Area of Trial

Advanced solid tumors with varying degrees of hepatic impairment

Approved Indication

Investigational

Study Number

CASA404A2105

Title

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

Phase of Development

I

Study Start/End Dates

23 Jul 2009 to 22 Feb 2010

Study Design/Methodology

This was a multi-center, open-label, dose-escalation study to assess the pharmacokinetics (PK) of a single intravenous dose of ASA404 in adult cancer patients with either impaired hepatic function (mild, moderate, and severe), or normal hepatic function. The study consisted of two phases, a Core Phase and an Extension Phase.

During the Core Phase of this study, hepatic impairment in study patients was categorized as mild, moderate or severe based upon the pre-dose (Day 1 Visit) total bilirubin level. These three categories of hepatic impairment were compared to a control group of cancer patients with normal hepatic function, giving a total of 4 groups.

Following the completion of the Core Phase, all enrolled patients were eligible to participate in the Extension Phase to receive up to a maximum of 12 (3-weekly or once every 3 weeks) cycles of ASA404 given either alone (for patients who were taxane ineligible based upon their type of cancer), or in combination with one of the following chemotherapy regimens: docetaxel, paclitaxel, carboplatin, or paclitaxel plus carboplatin. At the completion of Cycle 6, study drug administration continued for patients that had received benefit (Complete Response, Partial Re-

sponse or Stable Disease by Investigator's assessment) for a maximum of 12 cycles or until either progression of disease, unacceptable toxicities, withdrawal of patient consent or discontinuation of ASA404 development by Novartis, whichever occurred earlier.

The clinical development program of ASA404 was terminated early because two Phase III studies in patients with non-small cell lung carcinoma (ATTRACT I and ATTRACT II) showed no survival benefit between chemotherapy plus ASA404 and chemotherapy plus placebo arms. Therefore, this study (CASA404A2105) was prematurely terminated.

The study recruited only 5 patients at the time of termination, with 4 patients in the normal hepatic function group and 1 patient in the moderate hepatic impairment group. Therefore the main objectives of the study (i.e. to determine an ASA404 dose depending on the hepatic impairment level) could not be reached. Hence an abbreviated clinical study report (CSR) was prepared presenting results on safety variables.

Centers

Two centers in New Zealand

Publication

Not applicable

Objectives

Primary objective(s)

To evaluate the PK of a single intravenous dose (900, 1200, 1800 mg/m^2) of ASA404 in adult cancer patients with impaired hepatic function as compared to (cancer patients) controls with normal hepatic function

Secondary objective(s)

To assess the safety and tolerability of a single intravenous dose (900, 1200, 1800 mg/m^2) of ASA404 in adult cancer patients with impaired hepatic function as compared to (cancer patients) controls with normal hepatic function

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

During the Core Phase, ASA404 was administered as monotherapy in a single dose. During the Extension Phase, ASA404 was administered either as monotherapy (for patients who were taxane ineligible) or in combination with docetaxel, paclitaxel, carboplatin, or paclitaxel plus carboplatin.

A starting dose of ASA404 1200 mg/m^2 was selected for the normal, mild, and moderate hepatic impairment groups and a starting dose of ASA404 900 mg/m^2 was selected for the severe hepatic impairment group. The dose escalation schema was applied for the mild, moderate, and severe impairment groups, determined by the dose limiting toxicities (DLT) experienced by the hepatic-impaired groups. The DLT evaluation was not applied to the control group and the patients in this group received doses of 1200 mg/m^2 and 1800 mg/m^2.

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

Not Applicable

Criteria for Evaluation

Pharmacokinetic Evaluations

The following PK parameters characterizing the dispositions of ASA404 were to be derived from the individual plasma concentration versus time profiles:

$AUC_{(0\text{ -t last})}$ Area under curve (AUC) from time zero to the last measurable concentration sampling time (t_{last}) (mass x time x volume^{-1})

$AUC_{(0\text{-}\infty)}$ AUC from time zero to infinity (mass x time x volume^{-1})

C_{max} Maximum (peak) observed plasma drug concentration after single dose administration [mass x volume^{-1}]

t_{max} Time to reach maximum (peak) plasma drug concentration after single dose administration [time]

λ_z Smallest (slowest) disposition (hybrid) rate constant [time^{-1}] may also be used for terminal elimination rate constant [time^{-1}]

$t_{1/2}$ Elimination half-life associated with the terminal slope (λ_z) of a semi logarithmic concentration-time curve [time]. Use qualifier for other half-lives.

CL Total body clearance of drug from the plasma [volume x time-1]

Vz Apparent volume of distribution during terminal phase (associated with λ_z) [volume]

Due to premature study termination, the pharmacokinetic sample analysis was not completed. Therefore, no pharmacokinetic parameters were calculated and no analyses were reported.

Safety and tolerability

The assessment of safety was based mainly on the frequency of adverse events (AEs), number of abnormal laboratory values that were new or worsening based on the Common Toxicity Criteria for Adverse Events (CTCAE) Grade, physical examination, vital signs, performance status, electrocardiogram, weight, height and other measurements.

Other

Due to premature study termination, biomarkers (pharmacodynamic marker of ASA404 and angiogenesis markers) were not analyzed and no data were reported.

Statistical Methods

The following analysis sets were planned to be considered for the evaluation of this study.

Full Analysis Set (FAS): Included all adult cancer patients who passed the screening and were enrolled into the study. The summary tables of patient disposition, demographic and baseline characteristics and all listings used this analysis set.

Safety Set: Included all patients in the study who received at least one dose of ASA404 with a

valid post-baseline assessment. Tabulations of adverse events and safety listings used the Safety Set.

Patients who had received the dose of study drug but who had no post-treatment safety data of any kind were excluded from the safety set.

Formal statistical analysis was not performed for this study and only summary statistics are provided.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Patients having histologically-proven and radiologically-confirmed solid tumors, who were either refractory to standard chemotherapy or for whom treatment with an investigational agent alone (taxane ineligible) or in combination with docetaxel, paclitaxel, carboplatin, or paclitaxel plus carboplatin was appropriate
2. Age ≥18 years old
3. WHO Performance Status (PS) of 0-2
4. Laboratory values within the range, as defined below, within 2 weeks of starting study drug:
   - Absolute neutrophil count (ANC) >2.0 x 10^9/L
   - Platelets ≥75 x 10^9/L
   - Hemoglobin ≥10 g/dL
   - Creatinine Clearance according to Cockcroft-Gault formula ≥60 mL/minute
   - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.5 x ULN (≤5 x ULN if liver metastases) for patients that were assigned to Treatment Group 1 (Normal hepatic function) only
   - Alkaline phosphatase ≤2.5 x ULN for patients assigned to Treatment Group 1 (Normal hepatic function) only
   - Prothrombin Time (PT) ≤1.5 x ULN
   - Partial Thromboplastin time (PTT) ≤1.5 x ULN
   - Electrolyte values (potassium, calcium, magnesium) within the normal range. Patients with corrected electrolyte values are eligible
   - Total bilirubin ≤6 x ULN
   - Urinalysis that showed no evidence of proteinuria (≥ +2 or > 100 mg/dL on urine dipstick or hematuria (≥ +1 blood on urine dipstick)
5. A minimum of 4 weeks must have elapsed since the last treatment with endocrine therapy, immunotherapy, and chemotherapy and 6 weeks for nitrosoureas and Mitomycin C
6. Patients must have recovered from all acute radiotherapy-related toxicities
7. Females of child-bearing potential must have a negative serum pregnancy test at screening (confirmation of negative serum or urine pregnancy test within 72 hours prior to initial start of study drug on Day 1 and prior to each cycle in the Extension Phase)
8. Written informed consent obtained prior to any non-standard of care screening procedures being performed

Exclusion Criteria

1. Patients having CNS metastases. Patients having any clinical signs of CNS metastases must have a CT or MRI of the brain performed to rule out CNS metastases in order to be eligible for study participation. Patients who have had brain metastases surgically removed or irradiated with no residual disease confirmed by imaging are allowed
2. Patients with leptomeningeal metastatic disease
3. Patients with a history of another primary malignancy ≤5 years, with the exception of non-melanoma skin cancer or cervical cancer *in situ*
4. Major surgery ≤4 weeks prior to starting study drug. Major surgery is defined as any invasive operative procedure in which extensive resection is performed (e.g., a body cavity is entered, organs are removed, mesenchymal barrier is opened, an extensive orthopedic procedure is involved, or normal anatomy is significantly altered). Patients must have recovered from all acute surgery-related complications
5. Minor surgery ≤2 weeks prior to starting study drug. Minor surgery is defined as any invasive operative procedure in which only skin or mucous membranes and connective tissue are 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 is allowed. Patients must have recovered from all acute surgery-related complications
6. Concurrent use of other investigational agents and patients who have received investigational agents within 4 weeks (or longer if required by local regulation) prior to starting study drug
7. Prior exposure to vascular disrupting agents (VDA) 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 e.g. sorafenib, bevacizumab, etc. were allowed if they were within the timeframe specified in Inclusion criterion number 5
8. Patients with systolic BP < 100 mm Hg or > 160 mm Hg and/or diastolic BP < 60 mm Hg or >90 mm Hg
9. Patients with any one of the following:
    - Long QT syndrome
    - Screening 12-lead ECG QTc of >450 msec using the Friderica (QTcF formula) measurement determined per central ECG evaluation report
    - Myocardial infarction within 12 months of starting study drug
    - Unstable or poorly controlled angina pectoris, including Prinzmetal variant angina pectoris
    - History of a sustained ventricular tachycardia
    - History of ventricular fibrillation or torsade de pointes
    - 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

10. Other clinically significant heart disease (e.g., congestive heart failure (NY Heart Association class III or IV), uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
11. Concomitant use of drugs with a known risk of causing torsade de pointes or QTc prolongation. 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, whichever was longer) and able to switch to a protocol-permitted medication to treat their medical condition for the duration of their participation in the study
12. Concomitant use of any homeopathic or naturopathic medicines
13. 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 laboratory test (>5 mIU/mL)
14. Concurrent severe and/or uncontrolled medical disease (i.e. uncontrolled diabetes, chronic renal disease, confirmed diagnosis of HIV infection, or active uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with protocol
15. Significant neurologic or psychiatric disorder which could compromise participation in the study
16. History of gastrointestinal or rectal bleeding in the preceding 3 weeks of starting study drug
17. Acute renal disease (e.g., acute nephritis, nephrotic syndrome, acute tubular necrosis, glomerulonephritis, pyelonephritis, active hydronephrosis) and history of renal transplant
18. Symptoms (drowsiness, confusion, and asterixis) or history of Stage III or worse degree of encephalopathy within 3 months of study entry
19. History of surgical portosystemic shunt
20. Rapidly progressive liver disease (within the last 4 weeks) as indicated by liver transaminases, alkaline phosphatase, and GGT defined by an increase of at least 2 CTCAE grades, or a ≥50% worsening of serum bilirubin or prothrombin time
21. A positive Hepatitis B surface antigen (HBsAg)
22. Administration of CYP1A2 and CYP3A4/5 enzyme inducing or inhibiting drugs within 14 days prior to starting study drug. Use of these drugs was allowed during the Extension Phase.
23. Consumption of grapefruit, grapefruit juice, star fruit, star fruit juice or caffeinated beverages within 72 hours of starting study drug. Consumption was allowed during the Extension Phase
24. Donation or loss of 400 mL or more of blood within 4 weeks prior to starting study drug
25. 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 intrauterine device (IUD), oral or depot contraceptive or the barrier method plus spermicide
26. Patient unwilling or unable to comply with the protocol.
27. Patients receiving full-dose therapeutic oral or parenteral anticoagulation are ineligible. Patients receiving thrombolytic therapy within 10 days of starting are also ineligible. Patients

may receive prophylactic anticoagulation therapy for maintenance of the patency of vascular access devices

28. Known history of seizures requiring anti-convulsant therapy

In addition to the exclusion criteria above, patients who were to participate in the Extension Phase were excluded for the following reasons:

29. If patient will be treated with paclitaxel:
30. 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
31. Peripheral sensory neuropathy with functional impairment (CTCAE grade 2 neuropathy, regardless of causality)
32. Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions while taking paclitaxel and therefore are not considered effective contraceptive methods for this study when used as a single agent. Therefore, it is highly recommended that a concomitant barrier method be used with oral, implantable, or injectable contraceptives. The Investigator shall counsel the patient accordingly
33. If patient were treated with docetaxel
34. Known allergy or hypersensitivity to drugs formulated with polysorbate 80 or any known excipients of docetaxel

Number of Subjects

Patient disposition, by hepatic group and treatment (Full Analysis Set)

Disposition	Normal Control 1200 mg/m^2 (N=3), n (%)	Normal Control 1800 mg/m^2 (N=1), n (%)	Moderate Impairment 1200 mg/m^2 (N=1), n (%)	All subjects (N=5), n (%)
Enrolled	3 (100.0)	1 (100.0)	1 (100.0)	5 (100.0)
Entered Extension phase	3 (100.0)	1 (100.0)	1 (100.0)	5 (100.0)
Primary reason for end of treatment				
Adverse event(s)	1 (33.3)	1 (100.0)	0 (0.0)	2 (40.0)
Disease Progress	1 (33.3)	0 (0.0)	1 (100.0)	2 (40.0)
Administrative problems	1* (33.3)	0 (0.0)	0 (0.0)	1 (20.0)

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

*The study was terminated early and patient (NZL/0001/00005) was discontinued in extension phase

Demographic and Background Characteristics

Demographics and other baseline characteristics, by hepatic group (Full Analysis Set)

Demographic Variables	Normal control (N=4)	Moderate Impairment (N=1)	All Patients (N=5)
Age (years)			
n	4	1	5
Mean	65.3	63.0	64.8
SD	8.18		7.16
Median	64.0	63.0	63.0
Min	58	63	58
Max	75	63	75
Sex			
Male	3 (75.0%)	1 (33.3%)	4 (80.0%)
Female	1 (25.0%)	0 (0.0%)	1 (20.0%)
Race			
Caucasian	3 (75.0%)	1 (33.3%)	4 (80.0%)
Asian	1 (25.0%)	0 (0.0%)	1 (20.0%)
Ethnicity			
Chinese	1 (25.0%)	0 (0.0%)	1 (20.0%)
Other	3 (75.0%)	1 (33.3%)	4 (80.0%)
Weight (kg)			
n	4	1	5
Mean	71.00	59.20	68.64

SD	13.351		12.710
Median	69.40	59.20	61.80
Min	58.3	59.2	58.3
Max	86.9	59.2	86.9
Height (cm)			
n	4	1	5
Mean	167.5	173.0	168.6
SD	4.20		4.39
Median	167.0	173.0	168.0
Min	163	173	163
Max	173	173	173
BMI (Kg/ m^2)			
n	4	1	5
Mean	25.25	19.80	24.16
SD	4.535		4.623
Median	23.80	19.80	21.90
Min	21.9	19.8	19.8
Max	31.5	19.8	31.5
BSA (m^2)			
n	4	1	5
Mean	1.80	1.70	1.78
SD	0.183		0.164
Median	1.80	1.70	1.70
Min	1.6	1.7	1.6
Max	2.0	1.7	2.0

Notes: BMI (kg/m^2) = weight (kg) / height (m)^2.

BSA (m^2) = sqrt([height (cm) x weight (kg)]/ 3600)

Baseline is 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 pharmacokinetic sample analysis was not completed. Therefore, no pharmacokinetic parameters were calculated and no analyses were reported.

Secondary Objective Result(s)

Safety results are tabulated below.

Safety Results

Adverse events, regardless of study drug relationship, by primary system organ class, preferred term, and treatment group (Safety Set)

Primary system organ class **Preferred term**	**1200 mg/m^2** **(N=4)** **n (%)**	**1800 mg/m^2** **(N=1)** **n (%)**	**Total** **(N=5)** **n(%)**
Any preferred term			
Total	4 (100.0)	1 (100.0)	5 (100.0)
Blood and lymphatic system disorders			
Total	2 (50.0)	0 (0.0)	2 (40.0)
Febrile neutropenia	1 (25.0)	0 (0.0)	1 (20.0)
Neutropenia	1 (25.0)	0 (0.0)	1 (20.0)
Cardiac disorders			
Total	0 (0.0)	1 (100.0)	1 (20.0)
Tachycardia	0 (0.0)	1 (100.0)	1 (20.0)
Eye disorders			
Total	0 (0.0)	1 (100.0)	1 (20.0)
Vision blurred	0 (0.0)	1 (100.0)	1 (20.0)
Gastrointestinal disorders			
Total	2 (50.0)	1 (100.0)	3 (60.0)
Abdominal pain	1 (25.0)	1 (100.0)	2 (40.0)
Abdominal pain upper	1 (25.0)	0 (0.0)	1 (20.0)
Constipation	2 (50.0)	0 (0.0)	2 (40.0)
Diarrhoea	0 (0.0)	1 (100.0)	1 (20.0)
Dry mouth	0 (0.0)	1 (100.0)	1 (20.0)
Nausea	0 (0.0)	1 (100.0)	1 (20.0)
Stomatitis	1 (25.0)	0 (0.0)	1 (20.0)
Vomiting	1 (25.0)	1 (100.0)	2 (40.0)
General disorders and administration site conditions			
Total	3 (75.0)	1 (100.0)	4 (80.0)
Fatigue	3 (75.0)	1 (100.0)	4 (80.0)
Infusion related reaction	2(50.0)	0 (0.0)	2 (40.0)
Infusion site pain	1(25.0)	1(100.0)	2 (40.0)
Oedema peripheral	1 (25.0)	1(100.0)	2(40.0)
Pyrexia	0 (0.0)	1(100.0)	1(20.0)
Hepatobiliary disorders			
Total	1 (25.0)	0 (0.0)	1 (20.0)
Gallbladder enlargement	1 (25.0)	0 (0.0)	1 (20.0)

Infections and infestations			
Total	2 (50.0)	0 (0.0)	2 (40.0)
Cellulitis	1 (25.0)	0 (0.0)	1 (20.0)
Pneumonia	1 (25.0)	0 (0.0)	1 (20.0)
Rhinitis	1 (25.0)	0 (0.0)	1 (20.0)
Injury, poisoning and procedural Complications			
Total	1 (25.0)	1 (100.0)	2 (40.0)
Contusion	0 (0.0)	1 (100.0)	1 (20.0)
Scratch	1 (25.0)	0 (0.0)	1 (20.0)
Metabolism and nutrition disorders			
Total	0 (0.0)	1 (100.0)	1 (20.0)
Decreased appetite	0 (0.0)	1 (100.0)	1(20.0)
Dehydration	0 (0.0)	1 (100.0)	1(20.0)
Hypomagnesaemia	0 (0.0)	1 (100.0)	1(20.0)
Hyponatraemia	0 (0.0)	1 (100.0)	1(20.0)
Hypophosphataemia	0 (0.0)	1 (100.0)	1(20.0)
Musculoskeletal and connective Tissue disorders			
Total	3 (75.0)	1 (100.0)	4(80.0)
Arthralgia	2 (50.0)	0 (0.0)	2(40.0)
Back pain	0 (0.0)	1 (100.0)	1 (20.0)
Limb discomfort	1 (25.0)	0 (0.0)	1 (20.0)
Myalgia	1 (25.0)	0 (0.0)	1 (20.0)
Neck pain	1 (25.0)	0 (0.0)	1 (20.0)
Nervous system disorders			
Total	2 (50.0)	1 (100.0)	3 (60.0)
Dizziness	1 (25.0)	1 (100.0)	2 (40.0)
Dysgeusia	1 (25.0)	0 (0.0)	1 (20.0)
Neuropathy peripheral	0 (0.0)	1 (100.0)	1 (20.0)
Psychiatric disorders			
Total	0 (0.0)	1 (100.0)	1 (20.0)
Anxiety	0 (0.0)	1 (100.0)	1 (20.0)
Respiratory, thoracic and Mediastinal disorders			
Total	2 (50.0)	1 (100.0)	3 (60.0)
Cough	1 (25.0)	0 (0.0)	1 (20.0)
Dyspnoea	0 (0.0)	1 (100.0)	1 (20.0)
Hypoxia	0 (0.0)	1 (100.0)	1 (20.0)
Oropharyngeal pain	1 (25.0)	1 (100.0)	2 (40.0)
Pneumonitis	0 (0.0)	1(100.0)	1(20.0)
Skin and subcutaneous tissue disorders			
Total	2 (50.0)	0 (0.0)	2 (40.0)
Alopecia	2 (50.0)	0 (0.0)	2 (40.0)

Hyperhidrosis	1 (25.0)	0 (0.0)	1 (20.0)
Pruritus	1 (25.0)	0 (0.0)	1 (20.0)
Vascular disorders			
Total	0 (0.0)	1(100.0)	1(20.0)
Hypotension	0 (0.0)	1(100.0)	1(20.0)

Note: - Preferred terms are sorted within primary system organ class by descending order of frequencies, as reported in the Total column.

- Treatments reflect ASA404 dose level in the Core and Extension phases and may have been administered with or without chemotherapy.

- 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.

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

- An AE may be counted in more than one cycle if multiple start dates were recorded for that AE, hence the sum the total column cycles may exceed the total column.

COMMENT: can we add a short statement here describing the grade 3 and 4 AEs?

Serious Adverse Events and Deaths

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

No patients died during the study or at the 30-day follow-up period.

Two patients (both from the normal hepatic function group) experienced six serious adverse events in the extension study. One patient receiving ASA404 1200 mg/m^2 plus paclitaxel 175 mg/m^2, experienced serious adverse events of abdominal pain, hyponatremia, hypoxia and pneumonitis and the other patient receiving ASA404 1800 mg/m^2 dose plus docetaxel l75 mg/m^2 experienced febrile neutropenia and gallbladder enlargement.

Two patients treated with ASA404 1200 mg/m² plus docetaxel and ASA404 1800 mg/m² plus paclitaxel respectively had to discontinue study drug during the extension phase due to AEs (one due to fatigue and the other due to pneumonitis).

One patient on the 1200 mg/m2 dose of study drug in the extension phase required dose adjustments of docetaxel and delay of ASA404 due to AEs.

Other Relevant Findings

Due to premature study termination, biomarkers were not assayed. Therefore, no analyses of biomarkers were conducted and no data were reported.

Date of Clinical Trial Report 20 Oct 2011
Date Inclusion on Novartis Clinical Trial Results Database 7-Feb-2012
Date of Latest Update