Sponsor

Novartis

Generic Drug Name

HSP990

Therapeutic Area of Trial

Advanced solid malignancies.

Approved Indication

Investigational

Protocol Number

CHSP990A2101

Title

A phase I dose escalation, multi-center, open-label study of HSP990 administered orally in adult patients with advanced solid malignancies

Study Phase

Phase I

Study Start/End Dates

19-May-2009 to 19-Jul-2012

Study Design/Methodology

This was a phase I, first in man, dose escalation study to determine the MTD of HSP990 as a single agent, administered orally once or twice weekly for 28 day cycles, in patients with locally advanced or metastatic solid malignancies whose disease had progressed despite standard therapy or for whom no standard therapy exists. The **dose escalation phase** required ≥ 3 patients per cohort (although two patients without any

treatment-related Common Toxicity Criteria for Adverse Events (CTCAE) greater than Grade 1 were sufficient for a dose escalation decision). At the end of each treatment cohort, Novartis and investigators chose between further dose escalation, dose de-escalation, and/or expansion of recruitment into a particular cohort. The dose-escalation decision was guided by the recommendations of an adaptive Bayesian logistic regression model (BLRM) for dose escalation with overdose control (EWOC), using the dose-determining set, in combination with other information (dose-limiting toxicity [DLT] and other toxicity, electrocardiogram (ECG), PK and efficacy data). Dose escalation was to continue until identification of the MTD or PK futility (no significant increase in exposure despite increasing doses). Final selection of the MTD was based on the recommendations of the Bayesian model, plus other available safety and tolerability information. In the **dose expansion phase,** the MTD cohort was to be expanded by enrolling additional patients to a total of 22 patients to be evaluated for safety, tolerability, PK, and biologic activity of HSP990.

Centers

One center each in France, Spain, Canada

Publication

None

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

HSP990 1 mg, 2.5 mg, 20 mg, and 50 mg hard gelatin capsules, administered orally using a once weekly or twice weekly schedule, for treatment cycles of 28 days. HSP990 was taken with water in the morning, approximately 30 minutes after a light breakfast, followed by a 3-hour fasting period. The twice weekly dosing schedule required ≥72 hours between the two doses, with both doses taken within a 7-day period. The planned dose levels for the dose escalation were 2.5, 5, 10, 20, 40, 70, 110, 160, and 220 mg once weekly, and 15, 20, 25, 30, 35, 40, 45, and 50 mg twice weekly. Dose adjustments/interruptions were permitted in accordance with the protocol. Intra-patient dose escalation was not permitted within the first four cycles of treatment. Dosing started at 2.5 mg for the once weekly schedule and stopped at 60 mg in the once weekly regimen where 2/5 patients experienced DLTs. The MTD in this study was declared to be 50 mg administered once weekly, and a further 16 patients were recruited at that dose level in the expansion phase of the study. Dose escalation for the twice weekly dose regimen started with 25 mg and further escalation was possible, but the study stopped due to high inter-patient PK variability and lack of an efficacy trend across all dose groups.

Statistical Methods

The data were analyzed by Novartis using SAS Version 9.3, except for the BLRM, which was performed using R Version 2.8.1 and WinBUGS

Version 1.4.1. Data from participating centers in this protocol were combined to provide an adequate number of patients for analysis. Data from the dose expansion parts were pooled with the dose escalation data for the same dose. Data were summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant pharmacokinetic and pharmacodynamic measurements using descriptive statistics, i.e., mean, median, SD, min, max for continuous data and frequency count and percentage for categorical data. Medical history was summarized by MedDRA primary SOC and preferred term. Prior and concomitant medications and significant non-drug therapies were summarized by WHO ATC class (second level) and WHO preferred term. Antineoplastic medications since discontinuation of study drug were summarized by ATC class and preferred term. Adverse events were summarized by MedDRA primary system organ class, and preferred terms, and severity was assessed using CTCAE version 3.0. Pharmacokinetic parameters of HSP990 were estimated by non-compartmental methods (s) using WinNonlin® Pro (Version 5.2 - Pharsight, Mountain View, CA). Descriptive statistics (n, geometric and arithmetic means, SD, CV%, median and ranges) were presented for all primary (AUC_{inf}, AUC_{last}, C_{max}) and other ($t_{1/2}$, T_{max}, CL/F, V_z/F) PK parameters for each treatment group. An analysis of co-variance (ANOVA) was performed on log-transformed AUC and C_{max} (Cycle 1 Day 1, Cycle 1 Day 22) using a linear mixed effect model to assess day effect. Summary statistics for Hsp70 induction in PBMCs were tabulated. No analyses were performed of soluble or tumor-based biomarkers

The primary purpose of the dose-escalation phase was to determine the MTD of HSP990 when administered orally on a once weekly or a twice weekly schedule to adult patients with advanced solid malignancies that have progressed despite standard therapy or for which no standard therapy exists. Estimation of the MTD in the dose-escalation phase of the study was based upon the estimation of the probability of DLT in Cycle 1 for patients in the dose-determining set. For the once weekly regimen, a two-parameter Bayesian logistic regression model (BLRM) (Neuenschwander et al 2008) was used to model the dose-toxicity relationship and to compute the posterior probability of a DLT at each dose ($\pi_{(d)}$). The parametrization of the model was as follows:

$\text{logit}(\pi_{(d)}) = \log_e(\alpha) + \beta \log_e(d/d^*)$

where $\text{logit}(\pi_{(d)}) = \log_e(\pi_{(d)}/(1-\pi_{(d)}))$, and $\alpha, \beta > 0$. Doses were rescaled as d/d* where d* is the reference dose and as a consequence α is equal to the odds of the probability of toxicity at d* for the once weekly regiment. Note that for a dose equal to zero, the probability of toxicity is zero. For the twice weekly schedule, a covariate was added into the model as described above. The parameter associated to this covariate is denoted by γ. The model including the covariate is thus given by:

$\text{logit}(\pi_{(d)}) = \log_e(\alpha) + \beta \log_e(d/d^*) + \gamma * I(\text{schedule=twice weekly})$,

where I (schedule=twice weekly) takes the value 1 if the twice weekly schedule is used, and 0 otherwise.

No formal interim analysis was planned. However, the dose-escalation phase included review of data from the current cohort prior to selection of next dose level.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

Patients were eligible for enrollment in the study if they met all of the following inclusion criteria:

1. Patients with histologically confirmed, advanced malignant solid tumors whose disease had progressed on standard therapy or for whom no standard therapy exists
2. All patients must have had at least one measurable lesion as defined by RECIST. Irradiated lesions were only evaluable for disease progression
3. All patients must have had documented progressive disease before entering the study
4. Age: ≥ 18 years
5. World Health Organization (WHO) Performance Status ≤ 2
6. Life expectancy of ≥ 12 weeks
7. Patients must have had the following laboratory values:

- Absolute Neutrophil Count (ANC) ≥1.5 x 10^9/L
- Hemoglobin (Hgb) ≥9 g/dl
- Platelets ≥100 x 10^9/L
- Potassium within normal limits
- Total calcium (corrected for serum albumin) within normal limits
- Magnesium above lower normal limit
- Phosphorus within normal limits
- Aspartate aminostranferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) ≤ 2.5 x Upper Limit of Normal (ULN) or ≤ 5.0 x ULN if liver metastases are present
- Serum bilirubin ≤1.5 x ULN

- Serum albumin >2.5 g/dl
- Serum creatinine ≤1.5 x ULN or 24-hour clearance ≥ 50 mL/min
- Negative serum pregnancy test. The serum pregnancy test must be conducted prior to the first administration of HSP990 (≤ 72 hours prior to dosing) in all pre-menopausal women and women <2 years after the onset of menopause

8. Patients must have been able and willing to swallow capsules
9. Ability to understand the patient information and informed consent form and comply with the protocol
10. Signed and dated written informed consent was available

Exclusion Criteria

Patients were excluded from enrollment in the study if they met any of the following exclusion criteria:

1. Patients with present or history of central nervous system (CNS) metastasis. Patients without clinical signs or symptoms of CNS involvement were not required to have a computed tomography (CT)/magnetic resonance imaging (MRI) of the brain.
2. Prior treatment with any Hsp90 or histone deacetylase inhibitor compound.
3. Patients who had not recovered from side effects of previous systemic anticancer therapy to <CTCAE Grade 2 prior to the first dose
4. Patients identified to be "poor or intermediate CYP2C9 metabolizers" based on results from the Genotype Test
5. Patients who had received systemic anti-cancer treatment prior to the first dose of HSP990 within the following time frames:
    - Patients who had received cyclical chemotherapy within a period of time that was shorter than the cycle length used for that treatment (e.g., 6 weeks for nitrosourea, mitomycin-C) prior to starting study drug or who had not recovered from the side effects of such therapy
    - Patients who had received biologic therapy (e.g., antibodies) within a period of time that was ≤ 4 weeks prior to starting study drug or who had not recovered from the side effects of such therapy
    - Patients who had been treated with a continuous or intermittent small molecule therapeutic within a period of time that was ≤ 5 t1/2 or ≤ 4 weeks (whichever is shorter) prior to starting study drug or who had not recovered from the side effects of such therapy
    - Patients who had received any other investigational agents within a period of time that was ≤ 5 $t_{1/2}$ or less than the cycle length used for that treatment or ≤ 4 weeks (whichever was shorter) prior to starting study drug or who had not recovered from the side effects of such therapy
    - Patients who had received wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug or who had not recovered from side effects of such therapy.

- Patients who had undergone major surgery ≤ 2 weeks prior to starting study drug or who had not recovered from side effects of such therapy

6. Treatment with therapeutic doses of sodium warfarin (Coumadin) or Acenocumarol. Low doses of Coumadin (e.g., ≤ 2 mg/day for line patency) were permitted, however the patients were to be carefully monitored for international normalized ratio (INR).
7. Patients using medications that were CYP2C9 inhibitors and/or medications known to have QT prolongation effect and could not be switched or discontinued to an alternative drug prior to commencing HSP990 dosing.
8. Unresolved diarrhea ≥ CTCAE grade 2
9. Patients who did not have either an archival tumor sample available or readily obtainable in the course of the study or were unwilling to have a fresh tumor sample collected at baseline.
10. Pregnant or lactating women.
11. Fertile women of childbearing potential (WCBP) not using adequate contraception (abstinence, oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile). Male patients whose partners were WCBP, not using adequate contraception.
12. Acute or chronic liver disease.
13. Acute or chronic renal disease.
14. Impairment of gastrointestinal (GI) function or GI disease that could significantly alter the absorption of HSP990 (e.g. stomach or small bowel resection, ulcerative diarrhea, malabsorption, uncontrolled vomiting, diarrhea)
15. Other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes, active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol.
16. Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory).
17. Patients with a history of another primary malignancy that was clinically significant or required active intervention
18. Cardiac exclusion criteria:
    - History (or family history) of long QT syndrome.
    - Mean QTcF ≥ 480 msec on screening ECG
    - History of clinically manifest ischemic heart disease including myocardial infarction, or unstable angina ≤ 3 months prior to study start.
    - Left ventricular dysfunction (left ventricular ejection fraction [LVEF] ≤ 45%) by multiple gated acquisition scan (MUGA) or echocardiogram (ECHO)
    - Clinically significant ECG abnormalities including one or more of the following: left bundle branch block, right bundle branch block with left anterior hemiblock, or 3rd degree AV block

- History or presence of atrial fibrillation, atrial flutter or ventricular arrhythmias including ventricular tachycardia or Torsades de Pointes
- Clinically significant resting bradycardia (<50 beats per minute)
- Patients who were currently receiving treatment with any medication which had a relative risk of prolonging the QTcF interval and could not be switched or discontinued to an alternative drug prior to commencing HSP990 dosing.
- Obligate use of a cardiac pacemaker
- Other clinically significant heart disease (e.g., congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen).

Participant Flow

Patient disposition, by treatment (FAS)

	2.5 mg weekly N=3 n (%)	5 mg weekly N=5 n (%)	10 mg weekly N=7 n (%)	20 mg weekly N=6 n (%)	30 mg weekly N=5 n (%)	50 mg weekly N=22 n (%)	60 mg weekly N=5 n (%)	25 mg twice weekly N=11 n (%)	All patients N=64 n (%)
Patients treated									
Treatment discontinued	3 (100.0)	5 (100.0)	7 (100.0)	6 (100.0)	5 (100.0)	22 (100.0)	5 (100.0)	11 (100.0)	64 (100.0)
Primary reason for end of treatment									
Adverse Event (s)	0	0	0	1 (16.7)	0	5 (22.7)	2 (40.0)	1 (9.1)	9 (14.1)
Abnormal laboratory value (s)	0	0	0	0	0	0	0	0	0
Abnormal test procedure result (s)	0	0	0	0	0	0	0	0	0
Subject withdrew consent	0	0	0	0	0	0	0	1 (9.1)	1 (1.6)
Lost to follow-up	0	0	0	0	0	0	0	0	0
Administrative problems	0	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0	0

Disease progression	3 (100.0)	5 (100.0)	7 (100.0)	5 (83.3)	5 (100.0)	17 (77.3)	3 (60.0)	9 (81.8)	54 (84.4)
Protocol deviation	0	0	0	0	0	0	0	0	0

Baseline Characteristics

Demographic summary by treatment group (Full Analysis Set)

	2.5 mg weekly N=3 n (%)	5 mg weekly N=5 n (%)	10 mg weekly N=7 n (%)	20 mg weekly N=6 n (%)	30 mg weekly N=5 n (%)	50 mg weekly N=22 n (%)	60 mg weekly N=5 n (%)	25 mg twice weekly N=11 n (%)	All patients N=64 n (%)
Age (years)									
n	3	5	7	6	5	22	5	11	64
Mean	57.0	56.0	55.7	53.8	56.2	55.1	61.0	57.6	56.2
SD	5.29	15.52	12.24	9.64	7.79	12.30	6.40	9.60	10.61
Median	55.0	57.0	59.0	55.0	58.0	53.0	60.0	55.0	56.5
Minimum	53	37	32	39	45	25	54	44	25
Maximum	63	73	68	64	66	74	69	75	75
Age category (years) - n (%)									
<65	3 (100.0)	3 (60.0)	5 (71.4)	6 (100.0)	4 (80.0)	14 (63.6)	3 (60.0)	8 (72.7)	46 (71.9)
>=65	0	2 (40.0)	2 (28.6)	0	1 (20.0)	8 (36.4)	2 (40.0)	3 (27.3)	18 (28.1)
Sex - n (%)									
Female	1 (33.3)	4 (80.0)	4 (57.1)	5 (83.3)	2 (40.0)	10 (45.5)	5 (100.0)	5 (45.5)	36 (56.3)
Male	2 (66.7)	1 (20.0)	3 (42.9)	1 (16.7)	3 (60.0)	12 (54.5)	0	6 (54.5)	28 (43.8)
Predominant Race - n (%)									
Caucasian	3 (100.0)	4 (80.0)	6 (85.7)	6 (100.0)	5 (100.0)	21 (95.5)	5 (100.0)	11 (100.0)	61 (95.3)
Black	0	0	0	0	0	0	0	0	0
Asian	0	1 (20.0)	1 (14.3)	0	0	0	0	0	2 (3.1)
Native American	0	0	0	0	0	0	0	0	0
Pacific Islander	0	0	0	0	0	0	0	0	0
Other	0	0	0	0	0	1 (4.5)	0	0	1 (1.6)
Ethnicity - n (%)									

Hispanic/Latino	0	1 (20.0)	0	0	0	0	0	5 (45.5)	6 (9.4)
Chinese	0	1 (20.0)	0	0	0	0	0	0	1 (1.6)
Indian (Indian subcontinent)	0	0	0	0	0	0	0	0	0
Japanese	0	0	0	0	0	0	0	0	0
Other	3 (100.0)	3 (60.0)	7 (100.0)	6 (100.0)	5 (100.0)	22 (100.0)	5 (100.0)	6 (54.5)	57 (89.1)
Mixed Ethnicity	0	0	0	0	0	0	0	0	0
Height (cm)									
n	3	5	7	6	5	22	4	11	63
Mean	170.67	162.40	166.43	165.33	169.20	166.11	156.38	167.77	165.91
SD	10.599	4.722	13.939	10.191	10.569	8.968	1.250	6.338	9.097
Median	169.00	162.00	162.00	161.00	171.00	165.00	156.25	167.00	165.00
Minimum	161.0	158.0	149.0	157.0	157.0	150.0	155.0	157.0	149.0
Maximum	182.0	170.0	183.0	183.0	182.0	182.0	158.0	180.0	183.0
Weight (kg, at baseline)									
n	3	5	7	6	5	22	5	11	64
Mean	71.20	72.20	70.43	81.35	78.34	72.31	57.98	79.00	73.39
SD	11.972	15.623	19.651	35.205	17.495	16.770	8.121	15.162	18.523
Median	65.00	68.50	70.00	74.55	80.00	68.80	57.50	78.00	70.00
Minimum	63.6	57.0	44.0	45.0	51.0	44.8	47.0	57.3	44.0
Maximum	85.0	91.0	101.2	139.0	96.3	119.0	67.7	98.7	139.0
Weight (kg, at baseline) - n (%)									
<55	0	0	1 (14.3)	1 (16.7)	1 (20.0)	4 (18.2)	2 (40.0)	0	9 (14.1)
55 - <75	2 (66.7)	3 (60.0)	3 (42.9)	2 (33.3)	1 (20.0)	10 (45.5)	3 (60.0)	5 (45.5)	29 (45.3)
>=75	1 (33.3)	2 (40.0)	3 (42.9)	3 (50.0)	3 (60.0)	8 (36.4)	0	6 (54.5)	26 (40.6)
BMI (kg/m², at baseline)									
n	3	5	7	6	5	22	4	11	63
Mean	24.32	27.34	25.17	29.31	27.15	26.31	23.14	27.98	26.61
SD	1.464	5.672	5.169	11.246	4.557	6.687	3.630	4.588	6.152
Median	24.54	23.70	25.38	24.74	29.06	24.80	23.05	29.32	25.38
Minimum	22.8	22.5	18.6	18.0	20.7	16.5	18.8	20.4	16.5

Maximum	25.7	34.3	31.8	47.0	31.1	50.2	27.6	33.2	50.2
BSA (m^2, at baseline)									
n	3	5	7	6	5	22	4	11	63
Mean	1.85	1.82	1.81	1.92	1.93	1.83	1.58	1.93	1.85
SD	0.205	0.210	0.311	0.455	0.269	0.226	0.122	0.212	0.260
Median	1.76	1.81	1.87	1.90	2.02	1.80	1.57	1.89	1.83
Minimum	1.7	1.6	1.4	1.4	1.5	1.4	1.4	1.6	1.4
Maximum	2.1	2.1	2.3	2.6	2.2	2.3	1.7	2.2	2.6
LVEF (%, at baseline)									
n	3	5	7	6	5	22	5	11	64
Mean	69.67	67.80	67.57	64.00	63.80	67.05	73.60	69.55	67.69
SD	7.506	6.017	7.913	10.789	9.628	9.815	6.348	7.461	8.654
Median	70.00	70.00	65.00	65.50	58.00	65.00	74.00	70.00	69.00
Minimum	62.0	60.0	57.0	50.0	55.0	50.0	63.0	60.0	50.0
Maximum	77.0	74.0	79.0	75.0	77.0	84.0	79.0	86.0	86.0
WHO performance status, at baseline - n (%)									
0	0	4 (80.0)	2 (28.6)	5 (83.3)	3 (60.0)	9 (40.9)	3 (60.0)	3 (27.3)	29 (45.3)
1	3 (100.0)	1 (20.0)	4 (57.1)	1 (16.7)	2 (40.0)	13 (59.1)	2 (40.0)	8 (72.7)	34 (53.1)
2	0	0	1 (14.3)	0	0	0	0	0	1 (1.6)
3	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0

Outcome measures

Primary Outcome Result(s)

MTD of HSP990 as a single agent when administered orally

Established MTD	50 mg once weekly

Secondary Outcome Result(s)

Summary of best overall response, by treatment group (Full Analysis Set)

	2.5 mg weekly N=3 n (%)	5 mg weekly N=5 n (%)	10 mg weekly N=7 n (%)	20 mg weekly N=6 n (%)	30 mg weekly N=5 n (%)	50 mg weekly N=22 n (%)	60 mg weekly N=5 n (%)	25 mg twice weekly N=11 n (%)	All patients N=64 n (%)
Best overall response - n (%)									
Complete response (CR)	0	0	0	0	0	0	0	0	0
Partial response (PR)	0	0	0	0	0	0	0	0	0
Stable disease (SD)	1 (33.3)	0	2 (28.6)	3 (50.0)	0	10 (45.5)	2 (40.0)	7 (63.6)	25 (39.1)
Progressive disease (PD)	2 (66.7)	5 (100.0)	5 (71.4)	3 (50.0)	5 (100.0)	12 (54.5)	2 (40.0)	2 (18.2)	36 (56.3)
Unknown	0	0	0	0	0	0	1 (20.0)	2 (18.2)	3 (4.7)
Not assessed	0	0	0	0	0	0	0	0	0
Overall response rate (ORR) (CR or PR)									
Point estimate - n (%)	0	0	0	0	0	0	0	0	0
95% confidence interval *	(0.0%, 70.8%)	(0.0%, 52.2%)	(0.0%, 41.0%)	(0.0%, 45.9%)	(0.0%, 52.2%)	(0.0%, 15.4%)	(0.0%, 52.2%)	(0.0%, 28.5%)	(0.0%, 5.6%)
Disease control rate (DCR) (CR or PR or SD)									
Point estimate - n (%)	1 (33.3%)	0	2 (28.6%)	3 (50.0%)	0	10 (45.5%)	2 (40.0%)	7 (63.6%)	25 (39.1%)
95% confidence interval *	(0.8%, 90.6%)	(0.0%, 52.2%)	(3.7%, 71.0%)	(11.8%, 88.2%)	(0.0%, 52.2%)	(24.4%, 67.8%)	(5.3%, 85.3%)	(30.8%, 89.1%)	(27.1%, 52.1%)

* Exact binomial confidence intervals

Summary of primary PK parameters for plasma HSP990, by treatment group (PK analysis subset)

Treatment group	Statistics	AUCinf (ng.h/mL)	AUClast (ng.h/mL)	Cmax (ng/mL)
Profile day: Cycle 1 Day 1				

2.5 mg weekly (N=3)	n	3	3	3
	Mean (SD)	393.841 (76.5059)	309.245 (31.3738)	12.937 (4.2729)
	CV% mean	19.426	10.145	33.030
	Geo-mean	388.803	308.207	12.426
	CV% geo-mean	19.963	10.016	36.786
	Median	395.464	300.918	13.500
	Min, Max	316.54,469.52	282.87,343.94	8.41,16.90
5 mg weekly (N=5)	n	5	5	5
	Mean (SD)	915.088 (374.6248)	834.743 (373.4873)	24.480 (6.5404)
	CV% mean	40.939	44.743	26.717
	Geo-mean	856.810	770.103	23.818
	CV% geo-mean	42.434	47.843	26.306
	Median	907.533	822.724	21.300
	Min, Max	490.41,1506.20	407.60,1419.06	18.70,33.40
10 mg weekly (N=7)	n	7	7	7
	Mean (SD)	1992.822 (1072.5352)	1882.504 (1048.5256)	70.286 (29.9200)
	CV% mean	53.820	55.698	42.569
	Geo-mean	1744.091	1642.713	63.690
	CV% geo-mean	63.032	63.141	54.715
	Median	1866.110	1718.658	71.200
	Min, Max	662.69,3922.88	632.71,3860.63	26.10,106.00
20 mg weekly (N=6)	n	6	6	6
	Mean (SD)	4027.403 (2843.0320)	3666.668 (2715.1366)	128.817 (89.0899)
	CV% mean	70.592	74.049	69.160
	Geo-mean	3467.958	3127.524	112.000
	CV% geo-mean	59.796	61.018	56.719
	Median	3061.646	2669.169	95.450
	Min, Max	1894.06,9695.50	1812.91,9107.63	71.90,307.00
30 mg weekly (N=5)	n	5	5	5

	Mean (SD)	6142.016 (2427.7422)	5854.092 (2358.2040)	253.000 (83.1445)
	CV% mean	39.527	40.283	32.863
	Geo-mean	5792.383	5510.032	242.496
	CV% geo-mean	39.031	39.658	33.267
	Median	4830.215	4580.795	228.000
	Min, Max	3859.84,9789.94	3687.93,9407.35	169.00,368.00
50 mg weekly (N=22)	n	22	22	22
	Mean (SD)	10108.264 (10229.4949)	8407.554 (5569.1954)	495.591 (278.5554)
	CV% mean	101.199	66.240	56.207
	Geo-mean	7737.855	7084.114	430.327
	CV% geo-mean	75.135	62.880	59.609
	Median	6990.349	6252.646	464.500
	Min, Max	2452.25,50057.82	2342.13,22424.08	136.00,1320.00
60 mg weekly (N=5)	n	5	5	5
	Mean (SD)	9712.093 (4901.3678)	9404.929 (4939.3510)	699.600 (424.2903)
	CV% mean	50.467	52.519	60.648
	Geo-mean	8857.410	8540.248	594.389
	CV% geo-mean	49.597	50.360	75.371
	Median	8769.170	8111.250	607.000
	Min, Max	5607.24,17662.34	5493.77,17571.47	215.00,1370.00
25 mg twice weekly (N=11)	n	0	10	11
	Mean (SD)		12579.502 (4710.9018)	270.455 (125.4897)
	CV% mean		37.449	46.400
	Geo-mean		11825.626	248.969
	CV% geo-mean		38.244	42.883
	Median		11576.318	216.000

Min, Max	7188.25,20328.12	148.00,539.00

CV% =coefficient of variation (%) =(sd/mean)*100

CV% Geo-mean =sqrt (exp (variance for log transformed data)-1)*100

Safety Results

Incidence of adverse events by primary system organ class, and treatment group (Safety Set)

	2.5 mg weekly N=3 n (%)	5 mg weekly N=5 n (%)	10 mg weekly N=7 n (%)	20 mg weekly N=6 n (%)	30 mg weekly N=5 n (%)	50 mg weekly N=22 n (%)	60 mg weekly N=5 n (%)	25 mg twice weekly N=11 n (%)	All patients N=64 n (%)
Patients with at least one adverse event	3 (100.0)	5 (100.0)	7 (100.0)	6 (100.0)	5 (100.0)	22 (100.0)	5 (100.0)	11 (100.0)	64 (100.0)
Adverse events by primary system organ class									
Gastrointestinal disorders	3 (100.0)	4 (80.0)	6 (85.7)	6 (100.0)	5 (100.0)	20 (90.9)	5 (100.0)	10 (90.9)	59 (92.2)
General disorders and administration site conditions	2 (66.7)	5 (100.0)	6 (85.7)	4 (66.7)	4 (80.0)	18 (81.8)	5 (100.0)	9 (81.8)	53 (82.8)
Nervous system disorders	1 (33.3)	2 (40.0)	7 (100.0)	2 (33.3)	1 (20.0)	18 (81.8)	4 (80.0)	9 (81.8)	44 (68.8)
Musculoskeletal and connective tissue disorders	2 (66.7)	5 (100.0)	7 (100.0)	3 (50.0)	3 (60.0)	9 (40.9)	2 (40.0)	7 (63.6)	38 (59.4)
Metabolism and nutrition disorders	2 (66.7)	1 (20.0)	2 (28.6)	2 (33.3)	3 (60.0)	16 (72.7)	4 (80.0)	7 (63.6)	37 (57.8)
Investigations	2 (66.7)	1 (20.0)	5 (71.4)	3 (50.0)	0	14 (63.6)	3 (60.0)	8 (72.7)	36 (56.3)
Psychiatric disorders	1 (33.3)	0	2 (28.6)	2 (33.3)	3 (60.0)	16 (72.7)	3 (60.0)	8 (72.7)	35 (54.7)
Infections and infestations	1 (33.3)	1 (20.0)	4 (57.1)	3 (50.0)	3 (60.0)	6 (27.3)	2 (40.0)	4 (36.4)	24 (37.5)
Respiratory, thoracic and mediastinal disorders	1 (33.3)	0	4 (57.1)	4 (66.7)	1 (20.0)	8 (36.4)	2 (40.0)	4 (36.4)	24 (37.5)
Skin and subcutaneous tissue disorders	0	2 (40.0)	1 (14.3)	3 (50.0)	1 (20.0)	5 (22.7)	1 (20.0)	4 (36.4)	17 (26.6)

Hepatobiliary disorders	2 (66.7)	0	0	0	1 (20.0)	6 (27.3)	2 (40.0)	3 (27.3)	14 (21.9)
Renal and urinary disorders	0	2 (40.0)	2 (28.6)	2 (33.3)	0	3 (13.6)	1 (20.0)	3 (27.3)	13 (20.3)
Blood and lymphatic system disorders	0	0	3 (42.9)	1 (16.7)	1 (20.0)	4 (18.2)	0	2 (18.2)	11 (17.2)
Injury, poisoning and procedural complications	1 (33.3)	0	2 (28.6)	1 (16.7)	0	5 (22.7)	0	1 (9.1)	10 (15.6)
Cardiac disorders	0	0	0	3 (50.0)	2 (40.0)	1 (4.5)	1 (20.0)	0	7 (10.9)
Eye disorders	1 (33.3)	2 (40.0)	0	0	0	2 (9.1)	1 (20.0)	1 (9.1)	7 (10.9)
Vascular disorders	1 (33.3)	0	0	0	0	4 (18.2)	2 (40.0)	0	7 (10.9)
Reproductive system and breast disorders	0	0	1 (14.3)	1 (16.7)	0	2 (9.1)	1 (20.0)	1 (9.1)	6 (9.4)
Ear and labyrinth disorders	1 (33.3)	0	0	0	0	0	1 (20.0)	0	2 (3.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (33.3)	0	1 (14.3)	0	0	0	0	0	2 (3.1)
Congenital, familial and genetic disorders	0	0	0	1 (16.7)	0	0	0	0	1 (1.6)

Adverse events (AEs) by primary system organ class (SOC) are presented in descending order of frequency in the 'All patients' group
A patient with multiple events within a SOC is counted only once within that SOC
Only AEs occurring during treatment or within 28 days of the last study medication are included

Adverse events, regardless of study drug relationship, occurring in at least 5% of all patients by preferred term, and treatment group (Safety set)

	2.5 mg weekly N=3 n (%)	5 mg weekly N=5 n (%)	10 mg weekly N=7 n (%)	20 mg weekly N=6 n (%)	30 mg weekly N=5 n (%)	50 mg weekly N=22 n (%)	60 mg weekly N=5 n (%)	25 mg twice weekly N=11 n (%)	All patients N=64 n (%)
Patients with at least one adverse event	3 (100.0)	5 (100.0)	7 (100.0)	6 (100.0)	5 (100.0)	22 (100.0)	5 (100.0)	11 (100.0)	64 (100.0)
Adverse events by preferred term									
Diarrhoea	1 (33.3)	3 (60.0)	3 (42.9)	6 (100.0)	4 (80.0)	18 (81.8)	5 (100.0)	9 (81.8)	49 (76.6)
Asthenia	1 (33.3)	4 (80.0)	4 (57.1)	4 (66.7)	3 (60.0)	12 (54.5)	3 (60.0)	6 (54.5)	37 (57.8)
Nausea	1 (33.3)	1 (20.0)	2 (28.6)	4 (66.7)	1 (20.0)	12 (54.5)	2 (40.0)	5 (45.5)	28 (43.8)
Vomiting	1 (33.3)	2 (40.0)	2 (28.6)	2 (33.3)	1 (20.0)	11 (50.0)	4 (80.0)	3 (27.3)	26 (40.6)
Decreased appetite	2 (66.7)	0	2 (28.6)	1 (16.7)	2 (40.0)	9 (40.9)	3 (60.0)	6 (54.5)	25 (39.1)
Insomnia	0	0	1 (14.3)	0	2 (40.0)	12 (54.5)	2 (40.0)	6 (54.5)	23 (35.9)
Dizziness	1 (33.3)	2 (40.0)	2 (28.6)	1 (16.7)	1 (20.0)	10 (45.5)	1 (20.0)	4 (36.4)	22 (34.4)
Abdominal pain	2 (66.7)	1 (20.0)	3 (42.9)	5 (83.3)	1 (20.0)	6 (27.3)	1 (20.0)	2 (18.2)	21 (32.8)
Headache	0	0	3 (42.9)	2 (33.3)	0	6 (27.3)	1 (20.0)	4 (36.4)	16 (25.0)
Abdominal pain upper	2 (66.7)	0	0	2 (33.3)	0	6 (27.3)	1 (20.0)	2 (18.2)	13 (20.3)
Aspartate aminotransferase increased	1 (33.3)	0	1 (14.3)	1 (16.7)	0	4 (18.2)	2 (40.0)	4 (36.4)	13 (20.3)
Back pain	0	1 (20.0)	2 (28.6)	1 (16.7)	1 (20.0)	3 (13.6)	1 (20.0)	4 (36.4)	13 (20.3)
Constipation	0	1 (20.0)	3 (42.9)	1 (16.7)	2 (40.0)	3 (13.6)	2 (40.0)	1 (9.1)	13 (20.3)
Alanine aminotransferase increased	0	0	0	1 (16.7)	0	5 (22.7)	2 (40.0)	4 (36.4)	12 (18.8)
Tremor	0	0	0	0	0	6 (27.3)	3 (60.0)	3 (27.3)	12 (18.8)
Fatigue	1 (33.3)	1 (20.0)	1 (14.3)	0	1 (20.0)	3 (13.6)	2 (40.0)	2 (18.2)	11 (17.2)
Anaemia	0	0	3 (42.9)	1 (16.7)	1 (20.0)	4 (18.2)	0	1 (9.1)	10 (15.6)
Anxiety	1 (33.3)	0	0	1 (16.7)	1 (20.0)	5 (22.7)	1 (20.0)	1 (9.1)	10 (15.6)
Peripheral sensory neuropathy	0	0	3 (42.9)	1 (16.7)	0	2 (9.1)	0	4 (36.4)	10 (15.6)
Pyrexia	1 (33.3)	1 (20.0)	0	3 (50.0)	2 (40.0)	3 (13.6)	0	0	10 (15.6)

Ataxia	0	0	1 (14.3)	0	0	4 (18.2)	0	4 (36.4)	9 (14.1)
Blood alkaline phosphatase increased	0	0	1 (14.3)	1 (16.7)	0	5 (22.7)	1 (20.0)	1 (9.1)	9 (14.1)
Cough	1 (33.3)	0	1 (14.3)	2 (33.3)	1 (20.0)	2 (9.1)	1 (20.0)	1 (9.1)	9 (14.1)
Gamma-glutamyltransferase increased	0	0	2 (28.6)	1 (16.7)	0	3 (13.6)	1 (20.0)	2 (18.2)	9 (14.1)
Nasopharyngitis	0	1 (20.0)	1 (14.3)	1 (16.7)	1 (20.0)	3 (13.6)	1 (20.0)	1 (9.1)	9 (14.1)
Hypokalaemia	0	0	1 (14.3)	0	0	5 (22.7)	0	2 (18.2)	8 (12.5)
Chest pain	0	0	1 (14.3)	1 (16.7)	1 (20.0)	3 (13.6)	0	1 (9.1)	7 (10.9)
Dyspnoea	0	0	0	2 (33.3)	1 (20.0)	3 (13.6)	0	1 (9.1)	7 (10.9)
Dysuria	0	1 (20.0)	1 (14.3)	2 (33.3)	0	1 (4.5)	1 (20.0)	1 (9.1)	7 (10.9)
Oedema peripheral	1 (33.3)	0	0	0	1 (20.0)	2 (9.1)	1 (20.0)	2 (18.2)	7 (10.9)
Rash	0	1 (20.0)	0	2 (33.3)	1 (20.0)	2 (9.1)	0	1 (9.1)	7 (10.9)
Weight decreased	0	0	1 (14.3)	0	0	3 (13.6)	1 (20.0)	2 (18.2)	7 (10.9)
Hyperbilirubinaemia	2 (66.7)	0	0	0	0	0	1 (20.0)	3 (27.3)	6 (9.4)
Hypocalcaemia	0	0	0	1 (16.7)	0	2 (9.1)	1 (20.0)	2 (18.2)	6 (9.4)
Hypomagnesaemia	1 (33.3)	0	0	0	1 (20.0)	2 (9.1)	1 (20.0)	1 (9.1)	6 (9.4)
Muscle spasms	1 (33.3)	0	0	0	2 (40.0)	2 (9.1)	1 (20.0)	0	6 (9.4)
Urinary tract infection	0	0	2 (28.6)	1 (16.7)	0	0	1 (20.0)	2 (18.2)	6 (9.4)
Abdominal distension	1 (33.3)	0	0	2 (33.3)	0	0	0	2 (18.2)	5 (7.8)
Bone pain	1 (33.3)	2 (40.0)	2 (28.6)	0	0	0	0	0	5 (7.8)
Cerebellar syndrome	0	0	0	0	0	1 (4.5)	2 (40.0)	2 (18.2)	5 (7.8)
Confusional state	1 (33.3)	0	1 (14.3)	0	0	0	2 (40.0)	1 (9.1)	5 (7.8)
Dehydration	0	0	0	0	0	3 (13.6)	1 (20.0)	1 (9.1)	5 (7.8)
Electrocardiogram QT prolonged	0	1 (20.0)	0	0	0	4 (18.2)	0	0	5 (7.8)
Hepatomegaly	1 (33.3)	0	0	0	1 (20.0)	3 (13.6)	0	0	5 (7.8)
Hyponatraemia	1 (33.3)	0	0	0	0	1 (4.5)	2 (40.0)	1 (9.1)	5 (7.8)
Musculoskeletal chest pain	1 (33.3)	0	0	1 (16.7)	1 (20.0)	0	0	2 (18.2)	5 (7.8)
Pain in extremity	0	1 (20.0)	1 (14.3)	0	1 (20.0)	0	0	2 (18.2)	5 (7.8)
Arthralgia	0	1 (20.0)	1 (14.3)	1 (16.7)	0	0	1 (20.0)	0	4 (6.3)

Balance disorder	0	0	0	0	0	3 (13.6)	1 (20.0)	0	4 (6.3)
Blood creatinine increased	1 (33.3)	0	0	1 (16.7)	0	0	1 (20.0)	1 (9.1)	4 (6.3)
Chills	1 (33.3)	0	0	0	0	1 (4.5)	2 (40.0)	0	4 (6.3)
Cholestasis	0	0	0	0	1 (20.0)	2 (9.1)	1 (20.0)	0	4 (6.3)
Dysphagia	0	1 (20.0)	0	0	0	2 (9.1)	0	1 (9.1)	4 (6.3)
Hyperhidrosis	0	0	0	0	1 (20.0)	1 (4.5)	1 (20.0)	1 (9.1)	4 (6.3)
Musculoskeletal pain	0	0	0	0	0	2 (9.1)	0	2 (18.2)	4 (6.3)
Myalgia	0	1 (20.0)	1 (14.3)	0	1 (20.0)	1 (4.5)	0	0	4 (6.3)
Neck pain	0	0	1 (14.3)	1 (16.7)	0	2 (9.1)	0	0	4 (6.3)
Oropharyngeal pain	0	0	1 (14.3)	1 (16.7)	0	0	1 (20.0)	1 (9.1)	4 (6.3)
Procedural pain	0	0	0	1 (16.7)	0	2 (9.1)	0	1 (9.1)	4 (6.3)

Adverse events (AEs) by preferred term are presented in descending order of frequency in the 'All patients' group
A patient with multiple events within a preferred term is counted only once within that preferred term
Only AEs occurring during treatment or within 28 days of the last study medication are included medication are included

Number of patients who died or experienced other serious or clinically significant adverse events, by treatment group (Safety Set)

	2.5 mg weekly N=3 n (%)	5 mg weekly N=5 n (%)	10 mg weekly N=7 n (%)	20 mg weekly N=6 n (%)	30 mg weekly N=5 n (%)	50 mg weekly N=22 n (%)	60 mg weekly N=5 n (%)	25 mg twice weekly N=11 n (%)	All patients N=64 n (%)
Patients with serious or significant AEs									
Death on study or 28 days after last dose									
Total	1 (33.3)	0	0	0	0	3 (13.6)	1 (20.0)	1 (9.1)	6 (9.4)
Deaths due to study indication	1 (33.3)	0	0	0	0	3 (13.6)	1 (20.0)	0	5 (7.8)
Deaths due to other causes	0	0	0	0	0	0	0	1 (9.1)	1 (1.6)
SAE	2 (66.7)	1 (20.0)	3 (42.9)	2 (33.3)	2 (40.0)	11 (50.0)	1 (20.0)	4 (36.4)	26 (40.6)
Discontinued due to AE	0	0	0	1 (16.7)	0	5 (22.7)	2 (40.0)	1 (9.1)	9 (14.1)
Discontinued due to SAE	0	0	0	1 (16.7)	0	1 (4.5)	0	1 (9.1)	3 (4.7)

Other Relevant Findings
Date of Clinical Trial Report 28-Nov-2012
Date Inclusion on Novartis Clinical Trial Results Database 11-Jun-2013
Date of Latest Update