Sponsor

Novartis

Generic Drug Name

HSP990

Therapeutic Area of Trial

Advanced solid malignancies

Approved Indication

Investigational drug

Protocol Number

CHSP990A1101

Title

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

Phase of Development

I

Study Start/End Dates

24-Feb-2010 to 05-Jan-2012

Study Design/Methodology

This was a phase I, open-label dose escalation study in which HSP990 was administered orally on a once weekly schedule. During the dose escalation phase, only Japanese patients were enrolled to determine the maximum tolerated dose (MTD). A Bayesian logistic regression model (BLRM) with dose escalation with overdose control (EWOC) was used to determine the MTD. After determination of the MTD, at least 6 (maximum of 10) Korean patients were planned to be enrolled into the cohort expansion phase at the determined MTD.

As there was no clear efficacy trend per response evaluation criteria in solid tumors (RECIST), Novartis decided to permanently stop recruitment of study patients and to terminate the study early. The study was discontinued during the dose escalation phase before the determination of MTD in the Japanese patients. Furthermore, none of the Korean patients were enrolled as the cohort expansion phase was not started.

Centre

Japan (2)

Publication

None

Outcome measures

Primary objective

Primary outcome variable was the MTD, which was based on the probability of dose-limiting toxicities (DLTs) in Cycle 1.

Secondary objectives

- Efficacy: Response to treatment using RECIST criteria.
- Safety: Adverse events (AEs), serious adverse events (SAEs), laboratory evaluations, physical examination, vital signs, weight, performance status evaluation, electrocardiograms (ECGs), cardiac enzymes (including but not limited to troponin I or T, creatinine kinase [CK], and the creatinine kinase-MB [CK-MB]), cardiac imaging (multiple gated acquisition [MUGA] scan or echocardiogram), and neurological examination.
- Pharmacokinetics (PK): PK profiles and PK parameters of HSP990 on Cycle 1 Day 1 and 22.
- Pharmacodynamic biomarkers: Levels of specific biomarkers (mainly Hsp70) in pre-treatment and post-treatment peripheral blood mononuclear cells (PBMC) samples.

Note: As stated earlier this study was discontinued before MTD was determined as there was no clear trend in efficacy. Therefore, the primary objective and some of the secondary objectives were not achieved. The objectives for which results are available are reported in this CTRD.

Test Product, Doses, and Mode of Administration

HSP990 was provided as 1 mg, 2.5 mg, 20 mg, and 50 mg hard gelatin capsules. It was administered orally on a once weekly schedule. It was taken in the morning, approximately 30 minutes after a light breakfast, followed by a 3 hour fasting period. HSP990 capsules was taken with a glass of water and swallowed quickly, without chewing.

The starting dose in the dose escalation phase was 2.5 mg. The provisional dose escalation levels are described in the table below:

Provisional dose level

Dose level	mg total	Provisional dose level increments from previous dose (%)
1	2.5	Starting dose
2	5	100
3	10	100
4	20	100

5	40	100
6	70	75
7	110	57
8	160	45
9	220	38

At all dose levels, the BLRM permitted alterations in the dose increments based on the observed toxicities. It was possible for some dose levels to be skipped or for additional dose levels to be added during the course of the study.

Dose escalation was not to exceed a 100% increase from the current dose being studied. If clinically relevant toxicity of ≥ CTCAE grade 2 was observed and suspected to be related to HSP990 in more than one patient within the current cohort, the dose escalation was limited to ≤ 50% of the current dose as a rule.

All dose modifications were based on the worst preceding toxicity. One dose reduction was allowed. The dose reduction from dose level 1 (2.5 mg) was not permitted, and any patient who needed a dose reduction from dose level 1 (2.5 mg) was to discontinue the study.

Statistical Methods

The data were analyzed using SAS Version 9.3, except for the BLRM, which was performed using R Version 2.8.1 and WinBUGS Version 1.4.1.

Analysis sets

The FAS consisted of all patients who received at least one dose of HSP990. The safety set consisted of all patients who received at least one dose of HSP990 and had at least one valid post-baseline safety assessment. The dose-determining analysis set consisted of all patients from the safety set who either met the prespecified minimum exposure criterion and had sufficient safety evaluations, or discontinued earlier due to DLT.

The dose-determining analysis set was used for the determination of the MTD.

The PK analysis subgroup consisted of all patients who received at least one HSP990 dose in Cycle 1 and had at least one measurable post-dose HSP990 concentration.

Primary efficacy end point

The primary objective of this study was the determination of the MTD of HSP990.

The MTD was defined to be the highest drug dosage not causing medically unacceptable, DLT during the first cycle of treatment in more than 33% of the treated patients. A DLT was defined as an AE or abnormal laboratory value assessed to be clinically relevant, which occurred within 28 days following the first dose of HSP990 (Cycle 1) and met any of the criteria for cardiac, hematologic, renal, hepatic toxicities, and other AEs as defined in the protocol.

The primary analysis method was an adaptive BLRM guided by the EWOC principle, according to which, any dose of HSP990 that had more than 25% probability of the true DLT rate being in the

excessive toxicity category was not considered for the next dose cohort. The statistical model for this dose-escalation study was based on a 2-parameter BLRM.

Toxicity was assessed using the National Cancer Institute (NCI) Common Terminology Criteria for AEs, version 3.0. All DLTs recorded in cycle 1 were listed by treatment group.

Secondary efficacy end point

Objective response rate, the duration of overall response (Complete Response or Partial Response) and of overall complete response (CR) assessed by RECIST criteria. The best overall response was listed by treatment group across all tumor types.

Secondary safety end points

The assessment of safety was based mainly on the frequency of AEs and on the number of laboratory values that fell outside of pre-determined ranges.

All safety analyses were based on the safety analysis set except for the listing of DLTs for which the dose determining analysis set was used.

Pharmacokinetics

Pharmacokinetic parameters were determined using non-compartmental method(s) using Win-Nonlin® Pro (Version 5.2).

The parameters listed below were estimated and reported. For AUCinf, CL/F, and Vz/F values, those on only Cycle 1 Day 1 were reported.

Non-compartmental PK parameters

Term	Definition
AUCinf	The area under the plasma concentration-time curve from time zero to infinity (amount x time x volume^{-1})
AUClast	The area under the concentration-time curve from time zero to the time of the last measurable sample (amount x time x volume^{-1})
Cmax	The maximum (peak) plasma drug concentration (amount x volume^{-1}) within one doing interval
Tmax	The time to reach maximum (peak) plasma drug concentration after single dose administration (time)
Vz/F	Apparent volume of distribution during the terminal phase (volume)
CL/F	Apparent total clearance (volume x time^{-1})
T1/2	The elimination half-life associated with the terminal slope (z) of the terminal phase on a semilogarithmic concentration-time curve (time).
Rsq_ adj	Square of the correlation coefficient associated with lambda_z
lambda_z (kel)	Terminal elimination rate constant (time^{-1})
Tlast	Time point that corresponds to the last measurable concentration
Clast	The last observed quantifiable concentration (amount x volume^{-1})

Descriptive statistics (n, geometric and arithmetic means, SD, CV%, geo-mean CV%, median, and ranges) were presented for all primary (AUCinf, AUClast, Cmax) and secondary (CL/F, Vz/F,

T1/2) PK parameters for each treatment group. For Tmax (secondary PK parameter), median, minimum, and maximum were presented. Accumulation ratios for Cmax and AUClast of Cycle 1 Day 22 to Cycle 1 Day 1 were estimated. Based on the concentration data from Cycle 2 Day 1 (24~168 hours post-dose), the T1/2 values were also estimated.

All plasma concentrations below the LLOQ or missing data were labeled as such in the concentration data listings and treated as zero in summary statistics and for the calculation of PK parameters.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

- Patients with histologically or cytologically confirmed, advanced malignant solid tumors whose disease had progressed on standard therapy or who had no standard therapy available.
- All patients who had at least one measurable or non-measurable lesion as defined by RECIST. Irradiated lesions are only evaluable for disease progression.
- Age ≥ 18 years in Korea, and ≥ 20 years in Japan.
- World Health Organization (WHO) Performance Status of ≤ 2.
- Life expectancy of ≥ 12 weeks.
- Patients who had the following laboratory values:
  - Absolute neutrophil count ≥ 1.5 x 10^9/L
  - Hemoglobin ≥ 9 g/dL
  - Platelets ≥ 100 x 10^9/L
  - Potassium within institutional normal limits or correctable with supplements
  - Total calcium (corrected for serum albumin) within institutional normal limits or correctable with supplements
  - Magnesium within institutional normal limits or correctable with supplements
  - Phosphorus within institutional normal limits or correctable with supplements
  - AST and ALT ≤ 2.5 x upper limit normal (ULN), or if liver metastases were present, AST and ALT ≤ 5.0 x ULN
  - Serum total 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 was to be conducted prior to the first administration of HSP990 (≤ 7 days prior to dosing) in all pre-menopausal women and women < 2 years after the onset of menopause

Exclusion Criteria

- Patients with central nervous system (CNS) metastasis, or a history of CNS metastasis.

- Patients who received prior treatment of any Hsp90 or histone deacetylase (HDAC) inhibitor compound.
- Patients identified to be "poor or intermediate CYP2C9 metabolizers" (i.e., patients who were homozygous for the CYP2C9 *2 allele or patients who were homozygous or heterozygous for the CYP2C9 *3 allele) based on results of the Genotype Test.
- Patients who had not recovered from side effects of previous systemic anticancer therapy to less than Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 prior to the first dose of the study treatment.
- Patients who received the following systemic anti-cancer treatment prior to the first dose of HSP990 within the following time frames, or who had not recovered from the side effects of the treatment.
  - Cyclical chemotherapy within a period of time that was shorter than the end of the cycle length used for that treatment (e.g., 6 weeks for nitrosourea, mitomycin-C) prior to starting treatment with the study drug
  - Biologic therapy (e.g., antibodies) within 6 weeks prior to starting treatment with the study drug
  - Any other investigational drugs within a duration of ≤ 5 T1/2 or less than the cycle length used for that treatment or within 4 weeks (whichever is shorter) prior to starting treatment with the study drug
- Patients using medications of CYP2C9 inhibitors that were unable to be switched to an alternative drug or discontinued prior to commencing HSP990 dosing.
- Patients with 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.
- Patients with clinically significant heart disease.

Participant Flow

Patient disposition by treatment group (FAS)

Disposition Reason	HSP990 2.5 mg N=3 n (%)	HSP990 5 mg N=3 n (%)	HSP990 10 mg N=4 n (%)	HSP990 20 mg N=3 n (%)	HSP990 40 mg N=4 n (%)	All patients N=17 n (%)
Patients treated						
Treatment discontinued	3 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	17 (100.0)
Treatment ongoing[a]	0	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Primary reason for end of treatment						
Adverse event(s)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (5.9)
Withdrew consent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (5.9)
Disease progression	3 (100.0)	3 (100.0)	3 (75.0)	3 (100.0)	3 (75.0)	15 (88.2)
Study evaluation after completion of treatment						
Patients no longer being followed for study evaluation completion	3 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	17 (100.0)
Patients continuing to be followed for study evaluation completion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Primary reason for study evaluation completion						
Follow-up phase completed as per protocol	3 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	17 (100.0)

a: Patient ongoing at the time of the database lock 22-Mar-2012

Baseline Characteristics

Demographic summary by treatment group (FAS)

Demographics variable	HSP990 2.5 mg N=3	HSP990 5 mg N=3	HSP990 10 mg N=4	HSP990 20 mg N=3	HSP990 40 mg N=4	HSP990 All Patients N=17
Age (years) at screening						
N	3	3	4	3	4	17
Mean	59.3	63.0	60.5	48.0	59.8	58.4
SD	3.06	7.21	11.96	14.73	3.95	9.51
Median	60.0	61.0	59.5	45.0	61.0	61.0
Minimum	56.0	57.0	49.0	35.0	54.0	35.0
Maximum	62.0	71.0	74.0	64.0	63.0	74.0
Age category (years) at screening, n (%)						
<65	3 (100)	2 (66.7)	2 (50.0)	3 (100)	4 (100)	14 (82.4)

>=65	0 (0.0)	1 (33.3)	2 (50.0)	0 (0.0)	0 (0.0)	3 (17.6)
Sex, n (%)						
Male	3 (100)	2 (66.7)	2 (50.0)	1 (33.3)	2 (50.0)	10 (58.8)
Female	0 (0.0)	1 (33.3)	2 (50.0)	2 (66.7)	2 (50.0)	7 (41.2)
Predominant Race, n (%)						
Asian	3 (100)	3 (100)	4 (100)	3 (100)	4 (100)	17 (100)
Ethnicity, n (%)						
Japanese	3 (100)	3 (100)	4 (100)	3 (100)	4 (100)	17 (100)
Height (cm) at baseline						
N	3	3	4	3	4	17
Mean	170.3	162.5	158.8	163.3	164.3	163.6
SD	10.44	9.42	10.62	7.91	11.06	9.54
Median	175.0	158.2	161.6	161.2	168.0	164.7
Minimum	158.3	156.0	144.0	156.6	148.2	144.0
Maximum	177.5	173.3	168.0	172.0	173.2	177.5
Weight (kg) at baseline						
N	3	3	4	3	4	17
Mean	66.5	67.0	60.0	61.1	64.9	63.7
SD	12.72	11.20	18.34	5.43	12.79	11.92
Median	71.2	61.7	65.0	62.9	68.0	64.8
Minimum	52.1	59.5	33.6	55.0	48.4	33.6
Maximum	76.2	79.9	76.2	65.4	75.2	79.9
Body mass index (kg/m^2)						
N	3	3	4	3	4	17
Mean	22.7	25.3	23.3	22.9	23.8	23.6
SD	1.75	1.40	4.89	1.14	2.18	2.64
Median	23.2	25.4	25.0	22.4	23.6	23.9
Minimum	20.8	23.8	16.2	22.1	21.9	16.2
Maximum	24.2	26.6	27.0	24.2	26.2	27.0
WHO performance status, n (%)						
0	1 (33.3)	3 (100)	4 (100)	0 (0.0)	3 (75.0)	11 (64.7)
1	2 (66.7)	0 (0.0)	0 (0.0)	3 (100)	1 (25.0)	6 (35.3)

Body Mass Index: BMI (kg/m^2) = weight (kg, at baseline) / (height [m, at screening] **2)

WHO performance status: 0 = fully active, able to carry out all normal activity without restriction; 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 = ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; 3 = capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; 4 = completely disabled. Cannot carry out any selfcare. Totally confined to bed or chair; 5 = Dead

Disease characteristics by treatment group – Primary site of cancer (FAS)

	HSP990 2.5 mg N=3 n (%)	HSP990 5 mg N=3 n (%)	HSP990 10 mg N=4 n (%)	HSP990 20 mg N=3 n (%)	HSP990 40 mg N=4 n (%)	All Patients N=17 n (%)
Primary site of cancer						
Pancreas	0	0	1 (25.0)	0	0	1 (5.9)
Oesophagus	0	0	1 (25.0)	0	0	1 (5.9)
Stomach	1 (33.3)	0	0	0	0	1 (5.9)
Colon	1 (33.3)	0	0	0	0	1 (5.9)
Rectum	1 (33.3)	1 (33.3)	2 (50.0)	0	0	4 (23.5)
Uterus	0	0	0	1 (33.3)	0	1 (5.9)
Kidneys	0	0	0	0	1 (25.0)	1 (5.9)
Salivary gland	0	1 (33.3)	0	1 (33.3)	0	2 (11.8)
Gall bladder ducts	0	1 (33.3)	0	0	1 (25.0)	2 (11.8)
Other	0	0	0	1 (33.3)	2 (50.0)	3 (17.6)
Details of tumor histology/cytology						
Adenocarcinoma	2 (66.7)	1 (33.3)	3 (75.0)	1 (33.3)	2 (50.0)	9 (52.9)
Squamous cell carcinoma	0	0	1 (25.0)	0	0	1 (5.9)
Gastrointestinal stromal tumor	1 (33.3)	0	0	0	0	1 (5.9)
Cholangio carcinoma	0	1 (33.3)	0	0	0	1 (5.9)
In situ carcinoma	0	0	0	1 (33.3)	0	1 (5.9)
Other	0	1 (33.3)	0	1 (33.3)	2 (50.0)	4 (23.5)

Disease characteristics by treatment group – Histological grade (FAS)

	HSP990 2.5 mg N=3 n (%)	HSP990 5 mg N=3 n (%)	HSP990 10 mg N=4 n (%)	HSP990 20 mg N=3 n (%)	HSP990 40 mg N=4 n (%)	All Patients N=17 n (%)
Well differentiated	1 (33.3)	0	0	0	0	1 (5.9)
Moderately differentiated	1 (33.3)	1 (33.3)	4 (100.0)	0	2 (50.0)	8 (47.1)
Poorly differentiated	0	1 (33.3)	0	1 (33.3)	0	2 (11.8)
Unknown	1 (33.3)	1 (33.3)	0	2 (66.7)	2 (50.0)	6 (35.3)

Disease characteristics by treatment group – Stage at initial diagnosis (FAS)

	HSP990 2.5 mg N=3 n (%)	HSP990 5 mg N=3 n (%)	HSP990 10 mg N=4 n (%)	HSP990 20 mg N=3 n (%)	HSP990 40 mg N=4 n (%)	All Patients N=17 n (%)
Stage II	1 (33.3)	0	0	0	0	1 (5.9)
Stage II a	0	0	1 (25.0)	0	0	1 (5.9)
Stage III	0	1 (33.3)	1 (25.0)	0	1 (25.0)	3 (17.6)
Stage III b	0	0	1 (25.0)	0	0	1 (5.9)
Stage IV	2 (66.7)	1 (33.3)	0	3 (100.0)	3 (75.0)	9 (52.9)

Stage IV a	0	0	1 (25.0)	0	0	1 (5.9)
Stage IV b	0	1 (33.3)	0	0	0	1 (5.9)

Disease characteristics by treatment group – Time since diagnosis and current relapse (FAS)

	HSP990 2.5 mg N=3	HSP990 5 mg N=3	HSP990 10 mg N=4	HSP990 20 mg N=3	HSP990 40 mg N=4	All Patients N=17
Time since initial diagnosis (month, at first dose of drug)						
N	3	3	4	3	4	17
Mean	64.3	42.3	48.5	30.0	35.5	43.9
SD	38.18	10.97	13.03	1.73	25.04	22.02
Median	79.0	46.0	50.0	29.0	34.0	40.0
Minimum	21.0	30.0	34.0	29.0	7.0	7.0
Maximum	93.0	51.0	60.0	32.0	67.0	93.0
Time since initial diagnosis category (month, at first dose of drug), n (%)						
>= 6 to <12	0	0	0	0	1 (25.0)	1 (5.9)
>= 12 to <24	1 (33.3)	0	0	0	0	1 (5.9)
>= 24	2 (66.7)	3 (100.0)	4 (100.0)	3 (100.0)	3 (75.0)	15 (88.2)
Time since most recent recurrence/relapse (month, at first dose of drug)						
N	2	3	4	3	4	16
Mean	3.5	3.0	1.3	2.7	7.5	3.7
SD	3.54	2.00	0.50	2.08	7.68	4.42
Median	3.5	3.0	1.0	2.0	6.5	1.5
Minimum	1.0	1.0	1.0	1.0	1.0	1.0
Maximum	6.0	5.0	2.0	5.0	16.0	16.0
Time since most recent recurrence/relapse category (month, at first dose of drug), n (%)						
=<1	1 (33.3)	1 (33.3)	3 (75.0)	1 (33.3)	2 (50.0)	8 (47.1)
>1 to =<2	0	0	1 (25.0)	1 (33.3)	0	2 (11.8)
>2 to =<3	0	1 (33.3)	0	0	0	1 (5.9)
>4 to =<5	0	1 (33.3)	0	1 (33.3)	0	2 (11.8)
>5 to =<6	1 (33.3)	0	0	0	0	1 (5.9)
>6	0	0	0	0	2 (50.0)	2 (11.8)
Missing	1 (33.3)	0	0	0	0	1 (5.9)

Disease characteristics by treatment group – Others (FAS)

	HSP990 2.5 mg N=3 n (%)	HSP990 5 mg N=3 n (%)	HSP990 10 mg N=4 n (%)	HSP990 20 mg N=3 n (%)	HSP990 40 mg N=4 n (%)	All Patients N=17 n (%)
Types of lesions at baseline						
Target only	0	2 (66.7)	0	0	2 (50.0)	4 (23.5)
Both target and non-target	3 (100.0)	1 (33.3)	4 (100.0)	3 (100.0)	2 (50.0)	13 (76.5)
Current extent of cancer to be reported						
Yes	3 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	4 (100.0)	17 (100.0)

No	0	0	0	0	0	0
Site of metastases						
Lung	2 (66.7)	2 (66.7)	3 (75.0)	2 (66.7)	3 (75.0)	12 (70.6)
Liver	1 (33.3)	1 (33.3)	2 (50.0)	0	1 (25.0)	5 (29.4)
Para-aortic abdominal lymph nodes	0	0	2 (50.0)	1 (33.3)	0	3 (17.6)
Peritoneum	1 (33.3)	0	0	1 (33.3)	1 (25.0)	3 (17.6)
Bone	0	0	0	0	1 (25.0)	1 (5.9)
Bone, sternum and ribs	0	0	0	1 (33.3)	0	1 (5.9)
Other, specify	1 (33.3)	2 (66.7)	0	0	1 (25.0)	4 (23.5)

Outcome measures

Primary Outcome Results

The MTD was not determined. The study was discontinued before the determination of the MTD (during the dose escalation phase). There was no DLT occurrence in each dose group during the dose escalation phase.

Secondary Outcome Results

Efficacy: Disease response

None of the patients achieved complete or partial responses. Three patients in the 40 mg dose group and one patient each in 2.5 mg, 10 mg, and 20 mg dose groups had the best response of stable disease (SD).

Biomarker

In all patients, Hsp70 level increased after the administration of HSP990. The maximum dose group (i.e. 40 mg) had the highest value of Hsp70. But in dose groups less than 40 mg, no trend of dose-dependent increase was observed.

Pharmacokinetics

AUC of HSP990 generally increased dose proportionally over the dose range from 2.5 mg to 40 mg, whereas Cmax increased greater than dose proportionally at the higher dose range from 20 mg to 40 mg: mean AUCinf increased from 401 to 8120 h·ng/mL, mean AUClast increased from 316 to 7840 h·ng/mL, mean Cmax increased from 13.8 to 453 ng/mL on Day 1 of Cycle 1.

Ratios of geometric means (Day 22 / Day 1) for AUClast and Cmax were approximately 1 in all treatment groups, suggesting that there was no accumulation following weekly oral doses of HSP990. Mean T1/2 of all dose groups were similar with a range of 18.3 to 23.9 hours on Day 1 of Cycle 1. HSP990 exhibited large Vz values (mean 161 to 188 L), indicating an extensive tissue distribution.

Summary of primary PK parameters for plasma HSP990 by treatment group in Japanese patients (PK analysis subgroup)

Treatment group	Statistics	HSP990 2.5 mg N=3	HSP990 5 mg N=3	HSP990 10 mg N=4	HSP990 20 mg N=3	HSP990 40 mg N=4
Profile Day : Cycle 1 Day 1						
AUCinf (h·ng/mL)	n	2	2	4	3	4
	Mean (SD)	401 (101)	895 (222)	1510 (457)	3160 (1140)	8120 (4870)
	CV% mean	25.3	24.9	30.2	36.1	59.9
AUClast (h·ng/mL)	n	3	3	4	3	4
	Mean (SD)	316 (109)	837 (140)	1400 (415)	2930 (968)	7840 (5040)
	CV% mean	34.4	16.7	29.7	33.0	64.2
Cmax (ng/mL)	n	3	3	4	3	4
	Mean (SD)	13.8 (3.75)	28.8 (9.91)	62.2 (16.1)	129 (62.6)	453 (193)
	CV% mean	27.3	34.4	25.9	48.7	42.5
Profile Day : Cycle 1 Day 22						
AUClast (h·ng/mL)	n	3	3	3	3	4
	Mean (SD)	347 (194)	1000 (227)	1250 (62.1)	3540 (1050)	7620 (3610)
	CV% mean	56.0	22.6	4.98	29.8	47.3

Cmax (ng/mL)	n	3	3	3	3	4
	Mean (SD)	17.3 (11.7)	37.3 (13.7)	61.4 (14.1)	169 (33.5)	497 (113)
	CV% mean	67.7	36.8	23.0	19.9	22.8
Ratio of Geometric Means : Cycle 1 Day 22 / Cycle 1 Day 1						
AUClast (h·ng/mL)	Ratio of Geo-mean	1.0250	1.1928	1.0290	1.2088	1.0236
	90%CI for Ratio	[0.5416, 1.9399]	[0.8723, 1.6311]	[0.8201, 1.2912]	[0.9391, 1.5559]	[0.8568, 1.2229]
Cmax (ng/mL)	Ratio of Geo-mean	1.1050	1.2866	0.9969	1.3886	1.1465
	90%CI for Ratio	[0.5129, 2.3806]	[0.9945, 1.6645]	[0.6817, 1.4577]	[0.6128, 3.1466]	[0.8424, 1.5603]

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

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

Summary of secondary PK parameters for plasma HSP990 by treatment group in Japanese patients (PK analysis subgroup)

Treatment group	Statistics	HSP990 2.5 mg N=3	HSP990 5 mg N=3	HSP990 10 mg N=4	HSP990 20 mg N=3	HSP990 40 mg N=4
Profile Day : Cycle 1 Day 1						
Tmax (h)	n	3	3	4	3	4
	Median	4.00	3.00	3.04	3.00	3.53
	[Min;Max]	[3.00;6.00]	[3.00;8.12]	[1.10;4.07]	[3.00;4.03]	[1.00;4.13]
CL/F (L/h)	n	2	2	4	3	4
	Mean (SD)	6.44 (1.63)	5.77 (1.43)	7.02 (1.79)	6.82 (2.09)	5.97 (2.38)
	CV% mean	25.3	24.9	25.4	30.7	39.8
Vz/F (L)	n	2	2	4	3	4
	Mean (SD)	170 (29.1)	161 (21.0)	188 (46.6)	175 (40.3)	165 (74.1)
	CV% mean	17.2	13.0	24.8	23.1	44.8
T1/2 (h)	n	3	3	4	3	4
	Mean (SD)	19.5 (2.07)	23.9 (7.47)	18.6 (0.702)	18.3 (3.39)	19.8 (5.11)
	CV% mean	10.6	31.3	3.77	18.5	25.8
Profile Day : Cycle 1 Day 22						
Tmax (h)	n	3	3	3	3	4
	Median	4.00	3.00	1.15	3.00	3.07
	[Min;Max]	[4.00;6.05]	[3.00;8.03]	[1.07;3.13]	[3.00;6.12]	[1.00;4.15]
T1/2 (h)	n	3	3	3	3	4
	Mean (SD)	17.8 (0.473)	22.6 (5.32)	16.4 (2.61)	16.3 (1.05)	20.3 (3.57)
	CV% mean	2.65	23.6	15.9	6.43	17.6

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

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

Safety Results

Adverse Events by System Organ Class (Safety Population)

Overall, 94.1% of patients reported one or more AEs, regardless of relationship to study drug. The most commonly associated SOCs overall were gastrointestinal disorders (58.8%), investigations (47.1%), metabolism and nutrition disorders (47.1%), and nervous system disorders (35.3%). All other SOCs were reported in less than 30% of patients. Nervous system disorders were more frequently reported in the 40 mg dose group than the other dose groups. The overall incidence of AEs of nervous system disorders was 100.0% in the 40 mg dose group, while that was 0.0% in the 20 mg dose group, 25.0% in the 10 mg dose group, 33.3% in the 5 mg dose group, and 0.0% in the 2.5 mg dose group.

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

Frequent adverse events (>= 10% by overall frequency), regardless of study treatment relationship, by preferred term and treatment group (Safety analysis set)

Preferred term	HSP990 2.5 mg N=3 n (%)	HSP990 5 mg N=3 n (%)	HSP990 10 mg N=4 n (%)	HSP990 20 mg N=3 n (%)	HSP990 40 mg N=4 n (%)	All Patients N=17 n (%)
-Total	2 (66.7)	3 (100.0)	3 (75.0)	3 (100.0)	4 (100.0)	15 (88.2)
Diarrhoea	0	2 (66.7)	0 (0.0)	1 (33.3)	3 (75.0)	6 (35.3)
Decreased appetite	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	2 (50.0)	4 (23.5)
Hypomagnesaemia	0 (0.0)	1 (33.3)	1 (25.0)	1 (33.3)	1 (25.0)	4 (23.5)
Nausea	0 (0.0)	1 (33.3)	1 (25.0)	1 (33.3)	1 (25.0)	4 (23.5)
Cough	0 (0.0)	1 (33.3)	1 (25.0)	1 (33.3)	0 (0.0)	3 (17.6)
Fatigue	0 (0.0)	1 (33.3)	1 (25.0)	1 (33.3)	0 (0.0)	3 (17.6)
Hyperkalaemia	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	3 (17.6)
Insomnia	0 (0.0)	0 (0.0)	1 (25.0)	1 (33.3)	1 (25.0)	3 (17.6)
Leukopenia	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	1 (25.0)	3 (17.6)
Rash	1 (33.3)	0 (0.0)	1 (25.0)	0 (0.0)	1 (25.0)	3 (17.6)
Activated partial thromboplastin time prolonged	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	2 (11.8)
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (11.8)
Dysgeusia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (11.8)
Extrapyramidal disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (11.8)
Nasopharyngitis	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	2 (11.8)
Neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (25.0)	2 (11.8)
Urticaria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (11.8)
Weight decreased	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (25.0)	2 (11.8)

Preferred terms are sorted by descending frequency in 'All patients' column.

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

A patient with multiple adverse events is counted only once in the total row.

Only AEs occurring during treatment or within 28 days of the last study medication are included.

Only AEs occurring in more than 10% frequency of all patients are included.

Frequent adverse events (>= 10% by overall frequency), suspected to be study drug related, by preferred term and treatment group (Safety analysis set)

Preferred term	HSP990 2.5 mg N=3 n (%)	HSP990 5 mg N=3 n (%)	HSP990 10 mg N=4 n (%)	HSP990 20 mg N=3 n (%)	HSP990 40 mg N=4 n (%)	All Patients N=17 n (%)
-Total	1 (33.3)	3 (100.0)	2 (50.0)	3 (100.0)	4 (100.0)	13 (76.5)
Diarrhoea	0 (0.0)	2 (66.7)	0 (0.0)	1 (33.3)	3 (75.0)	6 (35.3)
Decreased appetite	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	2 (50.0)	3 (17.6)
Hypomagnesaemia	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	1 (25.0)	3 (17.6)
Rash	1 (33.3)	0 (0.0)	1 (25.0)	0 (0.0)	1 (25.0)	3 (17.6)
Activated partial thromboplastin time prolonged	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	2 (11.8)
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (11.8)
Dysgeusia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (11.8)
Extrapyramidal disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (11.8)
Hyperkalaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (11.8)
Leukopenia	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (25.0)	2 (11.8)
Nausea	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (25.0)	2 (11.8)
Urticaria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (11.8)
Weight decreased	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (25.0)	2 (11.8)

Preferred terms are sorted in descending frequency of 'All patients' column.

Serious Adverse Events and Deaths

Deaths

No patients died during the study.

Serious adverse events

There were 8 SAEs regardless of relationship to study drug reported on study treatment period. Each event was reported only once in each patient.

Serious adverse events by treatment group

Treatment group	Adverse event (Preferred)	Start date[a] / Duration (days)	Grade	Relation to study drug[b]	Action taken[c]
HSP990 2.5 mg	Tumour haemorrhage	Day 3 / 5	2	Not susp	3, 5
	Electrocardiogram QT prolonged	Day 36 / 4	3	Susp	5
HSP990 5 mg	Aspartate aminotransferase increased	Day 50 / continuing	3	Not susp	4, 5
	Alanine aminotransferase increased	Day 50 / continuing	3	Not susp	4, 5
	Hyperbilirubinaemia	Day 50 / continuing	2	Not susp	4, 5
HSP990 10 mg	Pancreatitis	Day 2 / continuing	2	Not susp	2, 3, 5
HSP990 20 mg	Pulmonary haemorrhage	Day 30 / 6	2	Susp	3, 5
	Pneumonia	Day -12 / 6	3	Not susp	3, 5

a: Study day is relative to the first day of treatment (Day 1).

b: Relation to study drug (Not susp = not suspected, Susp = suspected)

c: Action taken (1 = study drug dosage adjusted / temporarily interrupted, 2 = study drug permanently discontinued due to this AE, 3 = concomitant medication taken, 4 = non-drug therapy given, 5 = hospitalization / prolonged hospitalization)

Other Relevant Findings

None

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Date of Latest Update