Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Afuresertib

Trial Indication(s)

Relapsed multiple myeloma (MM)

Protocol Number

115960/CASB183X1101

Protocol Title

An open-label, dose escalation, phase I study to evaluate the tolerability, safety and pharmacokinetics of afuresertib monotherapy in Japanese relapsed multiple myeloma patients

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

13-Aug-2014 to 14-Aug-2019

Reason for Termination

Internal development of afuresertib in all indications was halted

Study Design/Methodology

This was an open-label, dose-escalating, phase I study of afuresertib targeting relapsed MM patients after treated with the standard therapy. Initial dose was afuresertib 125 mg and dose escalation proceeded up to 200 mg. If a total of 2 or more DLTs were noted at any dose level, then further recruitment had to be stopped.

If a DLT occurs in any of 3 subjects enrolled to dose level, 3 more subjects would be added to the dose level for evaluating toxicity. If no DLT occurs in additional 3 subjects (i.e., 1 DLT out of 6 subjects enrolled at the dose level), new 3 subjects would be enrolled at next dose level.

DLT evaluation and the decision to escalate the dose were made at the dose escalation meeting for each dose level by the study team personnel based upon the available information on safety, tolerability including DLT evaluation by investigators.

Centers

Japan (5)

Objectives:

Primary objective(s)

- To investigate the tolerability of afuresertib as monotherapy in Japanese relapsed MM patients

Secondary objective(s)

- To evaluate safety profiles of afuresertib as monotherapy in Japanese relapsed MM patients.
- To evaluate anti-tumor activity of afuresertib as monotherapy in Japanese relapsed MM patients (for evaluable patients only).

- To evaluate PK of afuresertib as monotherapy in Japanese relapsed MM patients.

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

Afuresertib was supplied to the investigators as 25 mg and 100 mg capsules, 50 mg and 75 mg film coated tablets by sponsor

Statistical Methods

There were no treatment regimen comparisons in this study. All analyses were descriptive.

All Subjects Population comprised all subjects who were given a subject ID in eCRF. All Treated. Subjects Population was defined as all subjects who received at least one dose of afuresertib. PK population consisted of all subjects from All Treated Subjects Population for whom a PK sample was obtained and analyzed. All analyses were presented by dose level and overall.

Demographic characteristics and other baseline characteristics including disease history were summarized. All Treated Subjects population was used for subject disposition, demographics and other baseline characteristic summaries and listings.

Efficacy analyses were based on the All Treated Subjects population. The overall response rate, defined as the percentage of subjects with stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR), and the clinical benefit rate, defined as the percentage of subjects with minor response (MR) or better, was calculated. Subjects with unknown or missing response were treated as non-responder.

AEs were graded according to the CTCAE Version 4.0, and coded to PT and SOC using MedDRA dictionary version 20.0. An overview summary of AEs, including number percentages of subjects with any AEs regardless of relationship to study drug, AEs related to study drug, AEs leading to study discontinuation regardless of relationship to study drug, on-treatment death, and serious AEs were produced. Safety analyses were based on the All Treated Subjects population.

PK analyses were based on the Pharmacokinetic population. Concentrations of afuresertib and its metabolite GSK2166207 in plasma were listed and summarized by treatment group and nominal time. Individual plasma concentration-time profiles and

mean profiles of afuresertib and GSK2166207 by treatment group were plotted using actual elapsed time for individual plots and nominal time for mean profiles.

Study Population: Key Inclusion/Exclusion Criteria

Key inclusion criteria

1. Japanese females or males aged 20 years or older.
2. Histologically confirmed diagnosis of relapsed multiple myeloma.
3. Performance status score of 0 or 1 according to the Eastern Cooperative Oncology Group scale.
4. Relapsed after at least 1 line of systemic therapy. The preparative regimen (with or without total body irradiation) and subsequent autologous stem cell rescue used for an autologous stem cell transplant are considered as one line of therapy.

Key exclusion criteria

1. Chemotherapy, radiotherapy, immunotherapy or other anti-myeloma therapy within 28 days prior to enrolment. In addition, any toxicity (except alopecia) should be recovered to ≤ Grade 1 by National Cancer Institute - Common Terminology Criteria for Adverse Events, version 4.0.
2. Use of an investigational drug within 28 days or five half-lives, whichever is longer.
3. History of an allogenic stem cell transplant. For patients with history of autologous stem cell transplant, inclusion criteria 10 must be met.
4. History of PI3K/AKT inhibitors.
5. Current use of prohibited medication or patient who requires any of these medications during treatment with afuresertib.
6. Current use of oral corticosteroids, except inhaled or topical use.
7. Uncontrolled diabetes mellitus by diet, exercise or medicinal therapies including insulin, and with fasting serum glucose ≥ 130 mg/dL (≥ 7.28 mmol/L).
8. Use of anticoagulants other than low dose (prophylactic) anticoagulants for patient whose prothrombin time / international normalization ratio and activated partial thromboplastin time meet ≤ 1.5 x ULN.
9. Presence of active gastrointestinal disease or other condition that could affect gastrointestinal absorption (e.g. malabsorption syndrome) or predispose patient to gastrointestinal ulceration.
10. Any major surgery that required hospitalization within last four weeks.

11. Central nervous system malignancies, primary or metastatic.
12. Diagnosis of or treatment history for another malignancy within 2 years, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy.
13. History of known infection with human immunodeficiency virus.
14. Positive hepatitis B surface antigen or hepatitis B virus DNA. If negative for hepatitis B surface antigen and positive for both or either of hepatitis B core and hepatitis B surface antibodies, hepatitis B virus DNA needs to be negative.
15. Positive hepatitis C virus antibody
16. QTc > 450 msec or QTc > 480 msec for patients with bundle branch block The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF).
17. Other clinically significant electrocardiogram abnormalities, including 2nd or 3rd degree atrioventricular block.
18. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty or stenting or bypass grafting within the past six months.
19. Class III or IV heart failure as defined by the New York Heart Association functional classification system.

Participant Flow Table

Summary of Study Treatment Status (All Treated Subjects Population)

	Afuresertib 125mg (N=3)	Afuresertib 150mg (N=6)	Afuresertib 200mg (N=2)	Total (N=11)
DLT evaluation period				
Completed	3 (100%)	5 (83.3%)	2 (100%)	10 (90.9%)
Not completed	0	1 (16.7%)	0	1 (9.1%)
Treatment status				
Ongoing	0	0	0	0
Discontinued	3 (100%)	6 (100%)	2 (100%)	11 (100%)
Primary reason for treatment Discontinuation				
Subject had disease progression including death	3 (100%)	5 (83.3%)	1 (50.0%)	9 (81.8%)
Completed scheduled treatment	0	0	0	0
Adverse event	0	0	1 (50.0%)	1 (9.1%)
Protocol deviation	0	0	0	0
Study closed/terminated	0	0	0	0
Lost to follow-up	0	0	0	0
Investigator discretion	0	0	0	0
Decision by subject or proxy	0	1 (16.7%)	0	1 (9.1%)

Baseline Characteristics

Demographic summary (All Treated Subjects Population)

		Afuresertib 125mg (N=3)	Afuresertib 150mg (N=6)	Afuresertib 200mg (N=2)	Total (N=11)
Age (yrs)	n	3	6	2	11
	Mean	68.7	71.0	58.5	68.1
	SD	2.52	6.96	19.09	9.25
	Median	69.0	70.0	58.5	69.0
	Min.	66	64	45	45
	Max.	71	82	72	82
Age group (yrs)	<18	0	0	0	0
	18 - 64	0	1 (16.7%)	1 (50.0%)	2 (18.2%)
	65 - 74	3 (100%)	3 (50.0%)	1 (50.0%)	7 (63.6%)
	>=75	0	2 (33.3%)	0	2 (18.2%)
Sex	n	3	6	2	11
	Female	0	3 (50.0%)	1 (50.0%)	4 (36.4%)
	Male	3 (100%)	3 (50.0%)	1 (50.0%)	7 (63.6%)
Race	n	3	6	2	11
	Asian - Japanese	3 (100%)	6 (100%)	2 (100%)	11 (100%)
Height (cm)	n	3	6	2	11
	Mean	163.7	157.3	156.5	158.9
	SD	5.51	10.39	6.36	8.57
	Median	164.0	154.5	156.5	158.0
	Min.	158	148	152	148
	Max.	169	174	161	174
Weight (kg)	n	3	6	2	11
	Mean	70.43	59.98	62.25	63.25
	SD	4.960	13.581	0.636	10.921
	Median	70.80	58.70	62.25	64.90

		Afuresertib 125mg (N=3)	Afuresertib 150mg (N=6)	Afuresertib 200mg (N=2)	Total (N=11)
	Min.	65.3	44.8	61.8	44.8
	Max.	75.2	76.5	62.7	76.5

Primary Outcome Result(s)

Summary of Overall Best Response Assessed by Investigator (IMWG 2011 Criteria) (All Treated Subjects Population)

	Afuresertib 125mg (N=3)	Afuresertib 150mg (N=6)	Afuresertib 200mg (N=2)	Total (N=11)
Best Response				
Stringent complete Response (sCR)	0	0	0	0
Complete Response (CR)	0	0	1(50.0%)	1(9.1%)
Very good partial response (VGPR)	0	0	0	0
Partial response (PR)	1(33.3%)	0	0	1(9.1%)
Minor response (MR)	0	1(16.7%)	0	1(9.1%)
Stable disease	1(33.3%)	4(66.7%)	1(50.0%)	6(54.5%)
Progressive Disease (PD)	1(33.3%)	1(16.7%)	0	2(18.2%)
Not Evaluable	0	0	0	0
Overall Response Rate				
sCR+CR+VGPR+PR	1(33.3%)	0	1(50.0%)	2(18.2%)
95% Confidence Interval*	(0.8%, 90.6%)	(0.0%, 45.9%)	(1.3%, 98.7%)	(2.3%, 51.8%)
Clinical Benefit Rate				
sCR+CR+PR+VGPR+PR+MR	1(33.3%)	1(16.7%)	1(50.0%)	3(27.3%)
95% Confidence Interval*	(0.8%, 90.6%)	(0.4%, 64.1%)	(1.3%, 98.7%)	(6.0%, 61.0%)

*95% confidence interval is calculated by using exact method.

Secondary Outcome Result(s)

Summary of derived plasma afuresertib PK parameters (single dosing, Day -3) (Pharmacokinetic Population)

Dose	AUC(0-tau) (hr*ng/mL) [1]	AUC(0-t) (hr*ng/mL) [1]	Cmax (ng/mL) [1]	t1/2 (hr) [1]	tmax (hr) [2]
125 mg (N=3)	3660 (38.8) (n=3)	6700 (24.7) (n=3)	283 (25.4) (n=3)	53.7 (39.9) (n=2)	4.00 (3.92-5.95) (n=3)
150 mg (N=6)	4710 (29.1) (n=6)	8310 (27.6) (n=6)	407 (59.8) (n=6)	38.4 (36.8) (n=6)	3.50 (1.97-7.85) (n=6)
200 mg (N=2)	6230 (6.1) (n=2)	11800 (5.4) (n=2)	628 (8.2) (n=2)	34.5 (11.3) (n=2)	3.52 (3.00-4.03) (n=2)

[1] Geo-mean (Geo-CV%); Geo-CV% =100* Sqrt [exp(variance of natural logarithm transformed data)-1]
[2] Median (min-max)
AUC(0-tau) = AUC0-24h, AUC(0-t) = AUClast, t1/2 = HL_Lambda_z (apparent terminal half-life)

Summary of derived plasma afuresertib PK parameters (multiple dosing, Day 8) (Pharmacokinetic Population)

Dose	AUC(0-tau) (hr*ng/mL) [1]	AUC(0-t) (hr*ng/mL) [1]	Cmax (ng/mL) [1]	t1/2,eff (hr) [1]	tmax (hr) [2]	Ro [1]
125 mg (N=3)	12400 (20.0) (n=3)	12400 (20.3) (n=3)	1060 (11.5) (n=3)	47.0 (42.3) (n=3)	4.00 (3.95-4.07) (n=3)	3.39 (33.9) (n=3)
150 mg (N=6)	16400 (33.4) (n=5)	16200 (29.6) (n=6)	1120 (35.7) (n=6)	46.1 (18.7) (n=5)	4.03 (3.08-6.07) (n=6)	3.30 (15.3) (n=5)
200 mg (N=2)	29000 (19.1) (n=2)	28900 (19.5) (n=2)	2140 (4.6) (n=2)	68.5 (29.1) (n=2)	2.94 (2.02-3.85) (n=2)	4.65 (25.7) (n=2)

[1] Geo-mean (Geo-CV%); Geo-CV% =100* Sqrt [exp(variance of natural logarithm transformed data)-1]
[2] Median (min-max)
AUC(0-tau) = AUC0-24h, AUC(0-t) = AUClast , Ro = (AUC0-24h on Cycle 1 Day 8)/(AUC0-24h on Cycle 0), t1/2,eff = ln2 • 24/ ln(Ro / (Ro-1)) [effective half-life based on drug accumulation at steady-state]

Summary of derived plasma GSK2166207 PK parameters (single dosing, Day -3) (Pharmacokinetic Population)

Dose	AUC(0-tau) (hr*ng/mL) [1]	AUC(0-t) (hr*ng/mL) [1]	Cmax (ng/mL) [1]	t1/2 (hr) [1]	tmax (hr) [2]
125 mg (N=3)	4920 (46.0) (n=3)	13900 (41.1) (n=3)	252 (37.1) (n=3)	59.3 (17.6) (n=2)	8.00 (8.00-24.0) (n=3)
150 mg (N=6)	7950 (16.3) (n=6)	21500 (14.5) (n=6)	397 (15.4) (n=6)	72.9 (32.8) (n=5)	7.82 (6.05-24.0) (n=6)
200 mg (N=2)	10100 (15.6) (n=2)	29300 (16.5) (n=2)	511 (14.6) (n=2)	NC (n=0)	24.0 (23.8-24.1) (n=2)

[1] Geo-mean (Geo-CV%); Geo-CV% =100* Sqrt [exp(variance of natural logarithm transformed data)-1]
[2] Median (min-max)
AUC(0-tau) = AUC0-24h, AUC(0-t) = AUClast, t1/2 = HL_Lambda_z (apparent terminal half-life)
NC: not calculated

Summary of derived plasma GSK2166207 PK parameters (multiple dosing, Day 8) (Pharmacokinetic Population)

Dose	AUC(0-tau) (hr*ng/mL) [1]	AUC(0-t) (hr*ng/mL) [1]	Cmax (ng/mL) [1]	t1/2,eff (hr) [1]	tmax (hr) [2]	Ro [1]
125 mg (N=3)	28600 (63.8) (n=2)	30800 (45.4) (n=3)	1470 (43.6) (n=3)	91.2 (3.2) (n=2)	5.77 (4.07-5.97) (n=3)	6.00 (2.9) (n=2)
150 mg (N=6)	37100 (32.8) (n=2)	38200 (23.6) (n=6)	1740 (20.0) (n=6)	72.8 (25.5) (n=2)	6.02 (4.00-7.98) (n=6)	4.90 (22.5) (n=2)
200 mg	NC	60000 (8.5)	2800 (5.3)	NC	5.88 (5.73-6.02)	NC

Dose	AUC(0-tau) (hr*ng/mL) [1]	AUC(0-t) (hr*ng/mL) [1]	Cmax (ng/mL) [1]	t1/2,eff (hr) [1]	tmax (hr) [2]	Ro [1]
(N=2)	(n=0)	(n=2)	(n=2)	(n=0)	(n=2)	(n=0)

[1] Geo-mean (Geo-CV%); Geo-CV% =100* Sqrt [exp(variance of natural logarithm transformed data)-1]
[2] Median (min-max)
AUC(0-tau) = AUC0-24h, AUC(0-t) = AUClast, Ro = (AUC0-24h on Cycle 1 Day 8)/(AUC0-24h on Cycle 0), t1/2,eff = ln2 * 24/ ln(Ro / (Ro-1)) [effective half-life based on drug accumulation at steady-state]

Safety Results

AEs Regardless of Relationship to Study Drug by PT (at least 2 subjects in any group) (All Treated Subjects Population)

	Afuresertib 125mg N=3		Afuresertib 150mg N=6		Afuresertib 200mg N=2		Total N=11	
PT	All grades n(%)	Grade >=3 n(%)	All grades n(%)	Grade >=3 n(%)	All grades n(%)	Grade >=3 n(%)	All grades n(%)	Grade >=3 n(%)
Number of subjects with at least one event	3 (100)	0 (0)	6 (100)	4 (66.7)	2 (100)	2 (100)	11 (100)	6 (54.5)
Diarrhoea	3 (100)	0 (0)	5 (83.3)	1 (16.7)	2 (100)	1 (50.0)	10 (90.9)	2 (18.2)
Stomatitis	2 (66.7)	0 (0)	2 (33.3)	0 (0)	1 (50.0)	0 (0)	5 (45.5)	0 (0)
Nausea	1 (33.3)	0 (0)	3 (50.0)	0 (0)	0 (0)	0 (0)	4 (36.4)	0 (0)
Decreased appetite	1 (33.3)	0 (0)	2 (33.3)	1 (16.7)	1 (50.0)	0 (0)	4 (36.4)	1 (9.1)
Rash	0 (0)	0 (0)	3 (50.0)	0 (0)	1 (50.0)	0 (0)	4 (36.4)	0 (0)
Pyrexia	1 (33.3)	0 (0)	2 (33.3)	0 (0)	0 (0)	0 (0)	3 (27.3)	0 (0)
Anaemia	0 (0)	0 (0)	3 (50.0)	3 (50.0)	0 (0)	0 (0)	3 (27.3)	3 (27.3)
Aspartate aminotransferase increased	0 (0)	0 (0)	1 (16.7)	0 (0)	2 (100)	1 (50.0)	3 (27.3)	1 (9.1)
Hyperglycaemia	0 (0)	0 (0)	3 (50.0)	0 (0)	0 (0)	0 (0)	3 (27.3)	0 (0)
Malaise	0 (0)	0 (0)	1 (16.7)	0 (0)	2 (100)	0 (0)	3 (27.3)	0 (0)
Eczema	2 (66.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (18.2)	0 (0)
Cough	0 (0)	0 (0)	2 (33.3)	0 (0)	0 (0)	0 (0)	2 (18.2)	0 (0)
Fatigue	0 (0)	0 (0)	2 (33.3)	0 (0)	0 (0)	0 (0)	2 (18.2)	0 (0)

Treatment-related AEs by PT (at least 2 subjects in any group) (All Treated Subjects Population)

	Afuresertib 125mg N=3		Afuresertib 150mg N=6		Afuresertib 200mg N=2		Total N=11	
PT	All grades n(%)	Grade >=3 n(%)	All grades n(%)	Grade >=3 n(%)	All grades n(%)	Grade >=3 n(%)	All grades n(%)	Grade >=3 n(%)
Number of subjects with at least one event	3 (100)	0 (0)	6 (100)	2 (33.3)	2 (100)	2 (100)	11 (100)	4 (36.4)
Diarrhoea	3 (100)	0 (0)	4 (66.7)	1 (16.7)	2 (100)	1 (50.0)	9 (81.8)	2 (18.2)
Stomatitis	2 (66.7)	0 (0)	2 (33.3)	0 (0)	1 (50.0)	0 (0)	5 (45.5)	0 (0)
Nausea	1 (33.3)	0 (0)	3 (50.0)	0 (0)	0 (0)	0 (0)	4 (36.4)	0 (0)
Decreased appetite	1 (33.3)	0 (0)	2 (33.3)	1 (16.7)	1 (50.0)	0 (0)	4 (36.4)	1 (9.1)
Rash	0 (0)	0 (0)	3 (50.0)	0 (0)	1 (50.0)	0 (0)	4 (36.4)	0 (0)
Pyrexia	1 (33.3)	0 (0)	2 (33.3)	0 (0)	0 (0)	0 (0)	3 (27.3)	0 (0)
Malaise	0 (0)	0 (0)	1 (16.7)	0 (0)	2 (100)	0 (0)	3 (27.3)	0 (0)
Fatigue	0 (0)	0 (0)	2 (33.3)	0 (0)	0 (0)	0 (0)	2 (18.2)	0 (0)

Serious adverse events by SOC and PT (All Treated Subjects Population)

SOC PT	Outcome	Maximum Grade	Action Taken with afuresertib	Related Study treatment	Afuresertib dose
Hepatobiliary disorders Liver dysfunction	Recovered/ Resolved	2	Dose Interrupted/ Delayed	Yes	150mg
Gastrointestinal disorders Diarrhoea	Recovered/ Resolved	3	Dose Interrupted/ Delayed	Yes	150mg
Infections and infestations Sepsis	Recovered/ Resolved	4	Not Applicable	No	150mg
Investigations Alanine aminotransferase increased	Recovered/ Resolved	3	Study Treatment Withdrawn	Yes	200mg

No deaths were reported during the study or within 30 days of the last dose of medication.

Conclusion:

Afuresertib was well tolerated up to 150 mg in Japanese subjects, which was supported by the clinical assessment of safety and Pharmakoknetics data. At dose of 200 mg, no Dose Limiting Toxicity assessed by investigators was reported though tolerability assessment was unavailable. Also, very preliminary activity of the study drug was indicated in some subjects.

Date of Clinical Study Report

CSR Published: 7 Apr 2020