Sponsor

Novartis

Generic Drug Name

Capmatinib

Trial Indication(s)

Not applicable

Protocol Number

CINC280A2103

Protocol Title

A phase I, multicenter, open-label, single-sequence drug-drug interaction study to assess the effect of INC280 on the pharmacokinetics of midazolam and caffeine in patients with cMET-dysregulated advanced solid tumors

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase II

Study Start/End Dates

10-Dec-2015 to 12-Sep-2017

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

A multicenter open-label, single-sequence study to assess the effect of capmatinib on the PK of midazolam and caffeine administered as a two-drug cocktail in patients with advanced MET-dysregulated solid tumors.
This study consisted of the following periods:

- Molecular pre-screening period: Patients with advanced solid tumors and with MET pathway dysregulation (MET mutations/amplifications or overexpression) were enrolled in this study. Molecular pre-screening for MET was determined by either local or central assessment.

- Screening/Baseline period: Baseline evaluations were performed within 28 days prior to the first dose of the probe drugs (midazolam and caffeine).
- Drug-drug interaction (DDI) phase (Day 1 to Day 12): A single oral dose of probe drugs was administered as a 2 drug cocktail on Day 1 and capmatinib was administered from Day 4 to Day 9. DDI was assessed after steady-state concentration was achieved for capmatinib (Day 9). PK sampling for midazolam, caffeine, and capmatinib were collected at various time points during DDI phase.
- Post-DDI phase (Day 13 and onward): After the completion of the DDI phase, patients were allowed to receive treatment with capmatinib tablets 400 mg bid, administered orally on continuous 21-day cycles until disease progression or discontinuation of study drug per protocol.
- Follow-up (safety and efficacy): Regardless of the reason for discontinuation from study treatment, patients were contacted for a safety follow-up 30 days after the last dose of capmatinib. At this time, the investigator recorded any AEs/SAEs that could have occurred after discontinuation of study treatment and/or follow up on resolution of ongoing AEs.

Centers

Eight centers in five countries: Bulgaria (1), Denmark (1), France (2), Spain (2), United Kingdom (2).

Objectives:

Primary objective: To evaluate the effect of multiple doses of capmatinib on the pharmacokinetics (PK) of a single oral dose of midazolam and caffeine in patients with MET-dysregulated advanced solid tumors.

Key secondary objective: To assess the safety and tolerability of capmatinib in patients with MET-dysregulated advanced solid tumors.

Other secondary objective: To evaluate the preliminary evidence of anti-tumor activity of capmatinib in patients with MET-dysregulated advanced solid tumors.

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

Study drug: oral tablets of capmatinib (INC280) 400 mg bid on Days 4 to 12 during DDI phase, afterwards 400 mg bid every day in continuous 21-day cycles.

Probe drugs: oral administration (syrup or solution or suspension) of Midazolam (2.5 mg) and oral tablets of caffeine (100 mg), single dose cocktail on Day 1 and Day 9 during DDI phase.

Statistical Methods

Analysis sets

The Full Analysis Set (FAS) and Safety Set included all patients in the study who received at least one dose of any study treatment (probe drugs or capmatinib). Three separate PK Analysis Sets (PAS) were considered for the evaluation of this study, one for each of the probe drugs (caffeine and midazolam) and one for capmatinib.

Pharmacokinetics

The respective PAS for each study treatment component was used for summaries (tables and figures). A formal statistical analysis was performed for AUClast, AUCinf, and Cmax of midazolam and caffeine. A linear mixed effect model was fitted to the log-transformed PK parameters (AUClast, AUCinf, and Cmax) to assess the effect of multiple doses of capmatinib on the PK of a single oral dose of 2.5 mg midazolam and 100 mg caffeine in patients with MET-dysregulated advanced solid tumors. Included in the model was treatment (probe alone, probe+capmatinib) as a fixed effect and patient as a random effect. For the analysis, probe+capmatinib were the test treatments and probe alone were the reference treatments. Point estimates of treatment differences and the corresponding 90% confidence intervals (CIs) were calculated and anti-logged to obtain the point estimates and 90% CIs for the geometric means ratio of the test versus reference on the original scale. For the time to reach maximum plasma concentration (Tmax), median and range of difference between treatments were provided.

Efficacy

Anti-tumor activity of capmatinib was presented by listing of tumor assessment, overall response and summary of best overall response (BOR) using FAS based on Investigator assessment (using RECIST v1.1). BOR was calculated as per RECIST v1.1 based on local Investigators' assessment of overall response at each tumor assessment. Overall response rate (ORR; the proportion of patients with a best overall response of Complete Response (CR) or Partial Response (PR)) and disease control rate (DCR; the proportion of patients with a best overall response of CR or PR or Stable Disease (SD)) were presented in the same table along with the exact 95% CIs.

Safety

Safety assessments consisted of evaluating adverse events (AEs) and serious adverse events (SAEs) (assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03), concomitant medications/therapies used to treat them, laboratory parameters, including hematology, chemistry, body weight, physical examinations, and ECG monitoring. Patients were assessed for safety while on the study and for 30 days after the last dose of study treatment.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

- Adult male or female patients

Patients must have:

- advanced solid tumors and confirmed MET dysregulation
- at least one measurable lesion as defined by RECIST 1.1.
- recovered from all toxicities related to prior anti-cancer therapies
- adequate organ function
- ECOG performance status (PS) of 0 or 1

Key Exclusion Criteria:

Patients must not have:

- known hypersensitivity to any of the excipients of capmatinib or to benzodiazepines or known intolerance and hypersensitivity to caffeine
- symptomatic central nervous system metastases
- presence or history of carcinomatous meningitis
- history of another primary malignancy that is currently clinically significant or currently requires active intervention
- clinically significant, uncontrolled heart diseases, including QTcF ≥ 450 msec (male patients), ≥ 460 msec (female patients) on the screening ECG
- thoracic radiotherapy to lung fields within 4 weeks prior to starting capmatinib
- major surgery within 4 weeks prior to starting capmatinib
- received unstable or increasing doses of corticosteroids
- impaired gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of capmatinib
- received or consumed, or are expected to receive or consume midazolam or caffeine-containing products (e.g. tea, coffee, cola), within two days prior to Day 1 and during the whole duration of the DDI phase (i.e. from Day -2 to Day 12);

Participant Flow Table (full analysis set)

Disposition/Reason	All patients N=37 n (%)
DDI pharmacokinetic phase	
Completed	33 (89.2)
Entered treatment phase	33 (89.2)
Discontinued from pharmacokinetic phase	4 (10.8)
Primary reason for discontinuation from pharmacokinetic phase	
Adverse event	2 (5.4)
Physician decision	1 (2.7)
Subject/guardian decision	1 (2.7)
Post-DDI treatment phase	
Discontinued from post-DDI treatment phase	33 (89.2)
Primary reason for discontinuation from treatment phase	
Progressive disease	22 (59.5)
Physician decision	5 (13.5)
Adverse event	2 (5.4)
Study terminated by sponsor[1]	2 (5.4)
Death	1 (2.7)
Subject/guardian decision	1 (2.7)

DDI: drug-drug interaction; FAS: full analysis set

[1] These two subjects were transferred to the rollover protocol for capmatinib

Baseline Characteristics (full analysis set)

Demographic Variable	All patients N=37
Age (years)	
n	37
Mean (StD)	59.5 (10.68)
Median (Min, Max)	60.0 (37, 75)
Age category (years) - n (%)	
<65	22 (59.5)
≥ 65	15 (40.5)
Sex -n (%)	
Female	19 (51.4)
Male	18 (48.6)
Race -n (%)	
White	36 (97.3)
Asian	1 (2.7)
Ethnicity -n (%) [1]	
Hispanic/Latino	9 (24.3)
Other	20 (54.1)
Unknown	8 (21.6)
Body surface area (m^2)	
n	37
Mean (StD)	1.86 (0.300)
Median (Min, Max)	1.80 (1.4, 2.7)
Body mass index (kg/m^2)	
n	37
Mean (StD)	25.76 (5.960)
Median (Min, Max)	24.35 (17.9, 47.4)
ECOG performance status - n (%)	
0	9 (24.3)
1	28 (75.7)

[1] Options for ethnicity were Hispanic or Latino, East Asian, Chinese, Japanese, Southeast Asian, South Asian, West Asian, Russian, Mixed ethnicity, Unknown, and Other

Summary of Pharmacokinetics

Primary Outcome Result(s)

Summary of midazolam primary PK parameters by treatment (pharmacokinetics analysis set)

Parameter	Statistics	Midazolam alone N=31	Capmatinib + midazolam N=31
AUCinf (ng*hr/mL)	n	30	31
	Mean (StD)	61.7 (40.4)	64.1 (30.9)
	CV%	65.5	48.2
	Geo-mean	53.5	58.3
	Geo-CV%	54.6	44.8
	Median	49.9	52.9
	Min, Max	19.6, 199	28.4, 167
AUClast (ng*hr/mL)	n	31	31
	Mean (StD)	59.5 (39.7)	62.2 (30.1)
	CV%	66.7	48.3
	Geo-mean	51.4	56.5
	Geo-CV%	55.0	45.4
	Median	48.2	52.1
	Min, Max	18.4, 197	27.9, 159
Cmax (ng/mL)	n	31	31
	Mean (StD)	19.6 (9.21)	23.4 (8.67)
	CV%	47.0	37.1
	Geo-mean	17.7	21.6
	Geo-CV%	47.5	45.5
	Median	18.0	22.6
	Min, Max	8.30, 46.9	6.71, 38.9

n = number of patients with corresponding evaluable PK parameters.
CV% = coefficient of variation (%) = StD/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.

Summary of statistical analysis of primary PK parameters for midazolam
(pharmacokinetics analysis set)

					Treatment comparison		
						90% CI	
PK parameter (unit)	**Treatment**	**n***	**Adjusted geo-mean**	**Comparison(s)**	**Geo-mean ratio**	**Lower**	**Upper**
AUCinf (ng*hr/mL)	midazolam	30	53.5				
	capmatinib + midazolam	31	58.3	capmatinib + midazolam/ midazolam alone	1.09	0.976	1.22
AUClast (ng*hr/mL)	midazolam	31	51.4				
	capmatinib + midazolam	31	56.5	capmatinib + midazolam/ midazolam alone	1.10	0.981	1.23
Cmax (ng/mL)	midazolam	31	17.7				
	capmatinib + midazolam	31	21.6	capmatinib + midazolam/ midazolam alone	1.22	1.07	1.38

Model is a linear mixed effects model of the log-transformed PK parameters. Included in the model were treatment as a fixed factor and patient as a random factor.
The results were back transformed to obtain adjusted geometric mean, geometric mean ratio, and 90% CI.
n* = number of observations used for the analysis.

Summary of caffeine primary PK parameters by treatment (pharmacokinetics analysis set)

Parameter	Statistics	Caffeine alone N=30	Capmatinib + caffeine N=30
AUCinf (ng*hr/mL)	n	30	26
	Mean (StD)	35200 (28800)	66400 (27000)
	CV%	81.9	40.6
	Geo-mean	28200	61100
	Geo-CV%	70.0	44.3
	Median	23500	64300
	Min, Max	10900, 128000	29800, 120000
AUClast (ng*hr/mL)	n	30	30
	Mean (StD)	33200 (25600)	65200 (27500)
	CV%	77.1	42.2
	Geo-mean	26900	59700
	Geo-CV%	69.2	45.6
	Median	22300	61600
	Min, Max	10300, 114000	27700, 124000
Cmax (ng/mL)	n	30	30
	Mean (StD)	3050 (792)	3210 (961)
	CV%	26.0	29.9
	Geo-mean	2950	3070
	Geo-CV%	26.5	30.9
	Median	3000	3130
	Min, Max	1900, 4570	1830, 5700

n = number of patients with corresponding evaluable PK parameters.
CV% = coefficient of variation (%) = StD/mean*100; geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.

Summary of statistical analysis of primary PK parameters for caffeine
(pharmacokinetics analysis set)

					Treatment comparison		
						90% CI	
PK parameter (unit)	**Treatment**	**n***	**Adjusted geo-mean**	**Comparison(s)**	**Geo-mean ratio**	**Lower**	**Upper**
AUCinf (ng*hr/mL)	caffeine alone	30	28200				
	capmatinib + caffeine	26	65900	capmatinib + caffeine/ caffeine	2.34	2.08	2.63
AUClast (ng*hr/mL)	caffeine alone	30	26900				
	capmatinib + caffeine	30	59700	capmatinib + caffeine/ caffeine	2.22	1.95	2.53
Cmax (ng/mL)	caffeine alone	30	2950				
	capmatinib + caffeine	30	3070	capmatinib + caffeine/ caffeine	1.04	0.964	1.13

Model is a linear mixed effects model of the log-transformed PK parameters. Included in the model were treatment as a fixed factor and patient as a random factor. The results were back transformed to get adjusted geometric mean, geometric mean ratio, and 90% CI.
n*= number of observations used for analysis.

Secondary Outcome Result(s)

Key secondary objective: Refer to Summary of Safety Results section

Other Secondary Outcome Result(s)

Summary of midazolam secondary PK parameters by treatment
(pharmacokinetics analysis set)

Parameter	Statistics	Midazolam alone N=31	Capmatinib + midazolam N=31
Tmax (hr)	n	31	31
	Mean (StD)	N/A	N/A
	CV%	N/A	N/A
	Geo-mean	N/A	N/A
	Geo-CV%	N/A	N/A
	Median	0.533	0.500
	Min, Max	0.350, 2.00	0.483, 1.00
T1/2 (hr)	n	30	31
	Mean (StD)	5.63 (2.47)	6.32 (2.87)
	CV%	43.9	45.5
	Geo-mean	5.14	5.72
	Geo-CV%	46.1	48.6
	Median	5.40	5.30
	Min, Max	2.14, 12.3	2.11, 12.7
Lambda_z (1/hr)	n	30	31
	Mean (StD)	0.148 (0.0669)	0.134 (0.0660)
	CV%	45.2	49.1
	Geo-mean	0.135	0.121
	Geo-CV%	46.1	48.6
	Median	0.129	0.131
	Min, Max	0.0565, 0.323	0.0544, 0.329
CL/F (L/hr)	n	30	31
	Mean (StD)	52.4 (24.8)	46.6 (18.3)
	CV%	47.4	39.4
	Geo-mean	46.7	42.9
	Geo-CV%	54.6	44.8
	Median	50.1	47.2
	Min, Max	12.6, 127	15.0, 87.9
Vz/F (L)	n	30	31
	Mean (StD)	384 (171)	383 (159)
	CV%	44.6	41.6
	Geo-mean	347	354
	Geo-CV%	50.0	41.8
	Median	358	346
	Min, Max	142, 753	143, 853

n: number of patients with corresponding evaluable PK parameters.
CV% = coefficient of variation (%) = StD/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.

Summary of caffeine secondary PK parameters by treatment
(pharmacokinetics analysis set)

Parameter	Statistics	Caffeine alone N=30	Capmatinib + caffeine N=30
Tmax (hr)	n	30	30
	Mean (StD)	N/A	N/A
	CV%	N/A	N/A
	Geo-mean	N/A	N/A
	Geo-CV%	N/A	N/A
	Median (range)	0.525 (0.350, 5.73)	0.700 (0.483, 11.8)
T1/2 (hr)	n	30	26
	Mean (StD)	8.22 (5.71)	17.0 (6.01)
	CV%	69.5	35.2
	Geo-mean	6.85	15.8
	Geo-CV%	64.1	44.9
	Median (range)	6.49 (2.62, 24.3)	17.7 (4.90, 27.3)
Lambda_z (1/hr)	n	30	26
	Mean (StD)	0.117 (0.0609)	0.0487 (0.0273)
	CV%	51.9	56.0
	Geo-mean	0.101	0.0439
	Geo-CV%	64.1	44.9
	Median (range)	0.107 (0.0286, 0.264)	0.0391 (0.0254, 0.141)
CL/F (L/hr)	n	30	26
	Mean (StD)	4.17 (2.19)	1.78 (0.766)
	CV%	52.5	42.9
	Geo-mean	3.54	1.64
	Geo-CV%	70.0	44.3
	Median (range)	4.25 (0.781, 9.16)	1.57 (0.832, 3.36)
Vz/F (L)	n	30	26
	Mean (StD)	36.1 (8.68)	39.1 (12.1)
	CV%	24.1	31.0
	Geo-mean	35.0	37.3
	Geo-CV%	25.2	32.5
	Median (range)	34.8 (21.0, 54.6)	38.7 (20.2, 69.0)

n: number of patients with corresponding evaluable PK parameters.
CV% = coefficient of variation (%) = StD/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.

Best overall response per Investigator assessment (full analysis set)

	All patients N=37	
	n (%)	**95% CI[a]**
Best overall response		
Complete response (CR)	1 (2.7)	
Partial response (PR)	1 (2.7)	
Stable disease (SD)	9 (24.3)	
Progressive disease (PD)	18 (48.6)	
Unknown [1]	8 (21.6)	
Overall response rate (ORR: CR+PR)	2 (5.4)	(0.7, 18.2)
Disease control rate (DCR: CR+PR+SD)	11 (29.7)	(15.9, 47)

N: The total number of patients in FAS. It is the denominator for percentage (%) calculation.
n: Number of patients who are at the corresponding category.
[1] Unknown are all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)
[a] Exact binomial 95% CI.

Summary of Safety

Safety Results

Adverse events regardless of study drug relationship by preferred term and maximum grade (at least 10% of patients) **(Safety set)**

	All patients N=37	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**
Any adverse event	37 (100)	22 (59.5)
Oedema peripheral	15 (40.5)	0
Nausea	14 (37.8)	0
Diarrhoea	10 (27.0)	0
Dyspnoea	10 (27.0)	2 (5.4)
Abdominal pain	9 (24.3)	1 (2.7)
Vomiting	9 (24.3)	0
Asthenia	8 (21.6)	1 (2.7)
Decreased appetite	8 (21.6)	0
Dyspepsia	8 (21.6)	0
General physical health deterioration	8 (21.6)	7 (18.9)
Headache	8 (21.6)	0
Blood creatinine increased	6 (16.2)	0
Fatigue	6 (16.2)	0
Hypoalbuminaemia	6 (16.2)	1 (2.7)
Anaemia	5 (13.5)	2 (5.4)
Abdominal pain upper	4 (10.8)	0
Ascites	4 (10.8)	2 (5.4)
Aspartate aminotransferase increased	4 (10.8)	0
Gamma-glutamyltransferase increased	4 (10.8)	1 (2.7)
Hyponatraemia	4 (10.8)	1 (2.7)

Preferred terms are sorted in descending frequency of 'All Grades' column, as reported under 'All Patients'.
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.
A patient with multiple severity grades for an AE while on treatment is only counted under the maximum grade.
Only AEs occurring during treatment or within 30 days of the last dose of study drug are reported.
Missing grades are included under ‘All grades’ column.
AEs are graded according to the CTCAE V4.03; MedDRA version 20.0 is used.

On-treatment deaths, by primary system organ class, and preferred term (Safety set)

Primary system organ class **Principal cause of death**	**All patients** **N=37** **n (%)**
Total on-treatment death	12 (32.4)
General disorders and administration site conditions	7 (18.9)
General physical health deterioration	5 (13.5)
Disease progression	2 (5.4)
Infections and infestations	1 (2.7)
Respiratory tract infection	1 (2.7)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2 (5.4)
Adenocarcinoma*	1 (2.7)
Penile cancer*	1 (2.7)
Nervous system disorders	1 (2.7)
Neurological decompensation*	1 (2.7)
Respiratory, thoracic and mediastinal disorders	1 (2.7)
Pleural effusion	1 (2.7)

Primary SOCs are presented alphabetically; PTs are sorted within primary SOC in descending frequency, as reported under 'All Patients'.
Deaths up to 30 days after the last dose are all included.
* Secondary to disease progression

Serious adverse events regardless of study drug relationship by preferred term and maximum grade (Safety set)

	All patients N=37	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**
Any serious adverse event	21 (56.8)	18 (48.6)
General physical health deterioration	7 (18.9)	7 (18.9)
Abdominal pain	2 (5.4)	0
Ascites	2 (5.4)	2 (5.4)
Constipation	2 (5.4)	1 (2.7)
Pleural effusion	2 (5.4)	1 (2.7)
Respiratory tract infection	2 (5.4)	2 (5.4)
Adenocarcinoma pancreas	1 (2.7)	1 (2.7)
Anaemia	1 (2.7)	1 (2.7)
Back pain	1 (2.7)	1 (2.7)
Bone pain	1 (2.7)	1 (2.7)
Diarrhoea	1 (2.7)	0
Hyperkalaemia	1 (2.7)	1 (2.7)
Hyponatraemia	1 (2.7)	1 (2.7)
Intestinal obstruction	1 (2.7)	1 (2.7)
Jugular vein thrombosis	1 (2.7)	1 (2.7)
Lung adenocarcinoma	1 (2.7)	1 (2.7)
Metastases to peritoneum	1 (2.7)	0
Neurological decompensation	1 (2.7)	1 (2.7)
Pneumothorax	1 (2.7)	1 (2.7)
Pyrexia	1 (2.7)	0
Respiratory failure	1 (2.7)	0
Thrombosis in device	1 (2.7)	1 (2.7)
Transitional cell carcinoma	1 (2.7)	0
Vomiting	1 (2.7)	0

Preferred terms are sorted in descending frequency of 'All Grades' column, as reported under 'All Patients'.
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.
A patient with multiple severity grades for an AE while on treatment is only counted under the maximum grade.
Only AEs occurring during treatment or within 30 days of the last dose of study treatment are reported.
Missing grades are included under ‘All grades’ column.
AEs are graded according to the CTCAE V4.03; MedDRA version 20.0 is used.

Other Relevant Findings

None

Conclusion:

The following conclusions can be drawn from this Phase I drug-drug interaction study to assess the effect of capmatinib on the PK of midazolam and caffeine administered as a two-drug cocktail in patients with advanced MET-dysregulated solid tumors :

- Capmatinib is not a CYP3A4 inhibitor.
- Capmatinib is a moderate CYP1A2 inhibitor.
- At a dose of 400 mg bid, capmatinib was generally well tolerated in this population with MET-dysregulated advanced solid tumors. AEs were manageable with appropriate treatment and supportive care. Overall the safety profile observed in this study is in line with the known safety profile for capmatinib.

Date of Clinical Trial Report

15-May-2018