NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis

Generic Drug Name

Capmatinib

Trial Indication(s)

MET dysregulated advanced solid tumors

Protocol Number

CINC280A2108

Protocol Title

A multicenter, open label, phase 1 dose escalation study to evaluate the pharmacokinetics, safety, and tolerability of INC280 tablet formulation with food in patients with cMET dysregulated advanced solid tumors.

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase I

Study Start/End Dates

Study Start Date: December 2016 (Actual)
Primary Completion Date: May 2018 (Actual)
Study Completion Date: May 2018 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a multicenter, open-label, Phase I dose-escalation study of capmatinib tablet formulation administered with food in subjects with MET dysregulated advanced solid tumors. This study was designed to determine the higher of the tolerated dose of capmatinib (300 mg or 400 mg bid), to assess the PK and safety of capmatinib with food.

(A) Dose-escalation phase: Capmatinib treatment was initiated at a dose of 300 mg bid with food on a continuous dosing schedule. A high-fat meal was given on the mornings of Cycle 1 Day 1 (C1D1) and Cycle 1 Day 7 (C1D7) to collect PK under high-fat condition. The dose-escalation decision was based upon Investigator and Sponsor consensus following review of safety and PK data during dose-escalation meetings (DEMs). During DEM, evaluation of safety and PK data of the 300 mg bid with food was confirmed well tolerated (with no incidence of DLTs), the next dose level cohort of 400 mg bid capmatinib with food was to be initiated.

(B) Expansion phase: At the completion of the dose-escalation phase, additional subjects were enrolled in the expansion phase at the higher tolerated dose of 400 mg bid with food to obtain 15 PK evaluable subjects. For safety considerations a minimum of 20 evaluable subjects at the higher tolerated dose of capmatinib was required.

Centers

12 centers in 8 countries: Sweden(4), Austria(1), Spain(2), Netherlands(1), United States(1), Germany(1), United Kingdom(1), Denmark(1)

Objectives:

Objectives	Endpoints
Primary	
1. To determine the higher of the tolerated dose of capmatinib tablets with food between 300 mg and 400 mg bid in subjects with MET dysregulated advanced solid tumors	1. Incidence, frequency and category of dose-limiting toxicities (DLTs) during the first 28 days of capmatinib treatment
2. To assess the PK of capmatinib with food	2. Plasma concentration and PK parameters, including but not limited to area under the concentration-time curve (AUC), maximum (peak) concentration of drug in plasma (Cmax), time to reach maximum (peak) plasma concentration after single dose administration (Tmax) for capmatinib and metabolite CMN288

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

Capmatinib was the investigational drug and is referred to as the “study drug” or “study treatment”. Capmatinib tablets were supplied at dose strengths of 100 mg and 200 mg. The treatment period began on C1D1 and a treatment cycle was defined as 21 days.

Treatment with capmatinib continued until subject experienced disease progression according to RECIST 1.1 as determined by the Investigator, unacceptable toxicity that precluded further treatment, death or if subject was lost to follow-up.

Statistical Methods

Primary variables: Estimation of probability of DLTs to determine higher of the tolerated dose

The primary endpoint for safety was estimation of the safe dose of capmatinib with food. The starting dose was 300 mg bid with food. The dose escalation to 400 mg was guided by the Bayesian logistic regression model (BLRM) of the estimation of probability of DLTs in the first 28 days of capmatinib treatment in the dose-determining set (DDS). A dose could only be used for newly enrolled subjects if the risk of excessive toxicity at that dose was less than 25%. A mixture prior distribution for the single-agent capmatinib model parameters was used consisting of a mixture of a meta-analytic-predictive (MAP) prior and a weakly informative prior. A recommended dose was identified based on other safety, clinical, PK, and pharmacodynamic data. All dosing decisions were guided by the escalation with overdose control (EWOC) principal.

Pharmacokinetics:

Endpoints for PK were plasma concentrations and PK parameters (AUClast, AUCtau, Cmax, Tmax) of capmatinib and CMN288. The PK parameters were derived based on the non-compartmental methods using WinNonlin® software version 6.4. The descriptive statistics were presented for concentrations at scheduled time points and for all PK parameters on C1D1 and C1D7 and using Full pharmacokinetic analysis set (PAS). All individual concentration-time profiles for capmatinib and CMN288 with median were displayed graphically on semi-log view using Safety set. In addition, the mean (± standard deviation) and geometric mean trough concentration-time profiles for capmatinib by dose arm over time were displayed graphically using PAS, and the mean (± standard deviation) and geometric mean concentration-time profiles for capmatinib and CMN288 over time were displayed graphically using Full PAS.

Study Population: Key Inclusion/Exclusion Criteria

Key inclusion criteria:
1. Subjects with a cytopathologically or histolopathologically confirmed diagnosis of an advanced solid tumor harboring MET dysregulation which had progressed despite standard therapy, or for which no standard therapy exists.
• MET dysregulation, determined either by local assessment or central assessment at a Novartis designated laboratory, was defined as at least one of the following:
a. MET amplification determined by fluorescent in situ hybridization (gene copy number ≥ 4).
b. MET overexpression determined by MET immunohistochemistry intensity score +3 in ≥ 50% of tumor cells.
c. MET mutation leading to exon 14 deletion.
2. Subjects had at least one measurable lesion as defined by RECIST version 1.1. A previously irradiated site lesion was counted as a target lesion if there was clear sign of progression since the irradiation.
3. Subjects had adequate organ function at the Screening visit.
4. Subject's Eastern Co-operative Oncology Group (ECOG) performance status was ≤ 1.

Key Exclusion Criteria:
1. Subjects who have had prior treatment with crizotinib, or any other MET or HGF inhibitor.
2. Subjects with symptomatic central nervous system (CNS) metastases who were neurologically unstable or required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS symptoms or carcinomatous meningitis.
3. Subjects with clinically significant, uncontrolled heart diseases.
4. Subjects who had undergone a major surgery (e.g., intra-thoracic, intra-abdominal or intra pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to starting capmatinib.
5. Subjects who received treatment with medications that met the following criterion and that cannot be discontinued at least 1 week

prior to the start of treatment with capmatinib and for the duration of the study: strong inducers of CYP3A4.
6. Pregnant or nursing (lactating) women.
7. Women of child-bearing potential.

Participant Flow Table

Treatment Phase

	INC280 300 mg BID	INC280 400 mg BID
Started	8	27
Dose Determining Set (DDS)	6	9
Pharmacokinetic Analysis Set (PAS)	7	25
Full PAS	7	24
Completed	0	0
Not Completed	8	27
Physician Decision	0	3
Study terminated by sponsor	0	3
Adverse Event	1	3
Death	0	1
Progressive Disease	6	17
Subject/guardian decision	1	0

Post-Treatment Follow-up Phase

	INC280 300 mg BID	INC280 400 mg BID
Started	1[1]	6[1]
Completed	0	0
Not Completed	1	6
Physician Decision	0	1
Death	0	1
Progressive Disease	1	3
New therapy for study indication	0	1

[1] Patients entering Post-Treatment Efficacy Fup Ph.

Baseline Characteristics

	INC280 300 mg BID	INC280 400 mg BID	Total
Number of Participants [units: participants]	8	27	35
Age Continuous (units: Years) Mean ± Standard Deviation			
	59.5±9.56	61.1±11.16	60.7±10.70
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)			

Female	4	11	15
Male	4	16	20
Race/Ethnicity, Customized (units: Participants)			
Caucasian	8	21	29
Unknown	0	6	6

Summary of Efficacy

Primary Outcome Result(s)

Incidence, frequency and category of Dose Limiting Toxiticities (DLTs)

	INC280 300 mg BID	INC280 400 mg BID
Number of Participants Analyzed [units: participants]	6	9
Incidence, frequency and category of Dose Limiting Toxiticities (DLTs) (units: Number of DLT)		
	0	0

Area Under the Plasma Concentration-time Curve From 0 to the Last Measurable Concentration (AUClast) for INC280 at Cycle 1 Days 1 and 7

	INC280 300 mg BID	INC280 400 mg BID

Number of Participants Analyzed [units: participants]	7	24
Area Under the Plasma Concentration-time Curve From 0 to the Last Measurable Concentration (AUClast) for INC280 at Cycle 1 Days 1 and 7 (units: ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)		
C1D1 (n= 7, 20)	6090 (59.9%)	12500 (42.7%)
C1D7 (n= 6, 20)	8660 (27.8%)	16800 (33.4%)

Area Under the Plasma Concentration-time Curve From 0 to the Last Measurable Concentration (AUClast) for metabolite CMN288 at Cycle 1 Days 1 and 7

	INC280 300 mg BID	INC280 400 mg BID
Number of Participants Analyzed [units: participants]	7	24
Area Under the Plasma Concentration-time Curve From 0 to the Last Measurable Concentration (AUClast) for metabolite CMN288 at Cycle 1 Days 1 and 7 (units: ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)		
C1D1 (n= 7, 20)	2640 (21.7%)	3370 (106.4%)
C1D7 (n= 6, 20)	2960 (31.2%)	3750 (74.0%)

Area Under the plasma Concentration time Curve From 0 to the end of a dosing interval (AUCtau) for INC280 at Cycle 1 Days 1 and 7

	INC280 300 mg BID	INC280 400 mg BID
Number of Participants Analyzed [units: participants]	7	24

Area Under the plasma Concentration time Curve From 0 to the end of a dosing interval (AUCtau) for INC280 at Cycle 1 Days 1 and 7 (units: ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)		
C1D1 (n= 3, 14)	6760 (27.2%)	13500 (28.0%)
C1D7 (n= 4, 15)	9370 (24.3%)	16800 (26.7%)

Area Under the plasma Concentration time Curve From 0 to the end of a dosing interval (AUCtau) for metabolite CMN288 at Cycle 1 Days 1 and 7

	INC280 300 mg BID	INC280 400 mg BID
Number of Participants Analyzed [units: participants]	7	24
Area Under the plasma Concentration time Curve From 0 to the end of a dosing interval (AUCtau) for metabolite CMN288 at Cycle 1 Days 1 and 7 (units: ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)		
C1D1 (n= 3, 9)	2690 (17.7%)	3340 (155.6%)
C1D7 (n= 5, 9)	3150 (33.0%)	3350 (105.5%)

Maximum Observed Plasma Concentration (Cmax) for INC280 at Cycle 1 Days 1 and 7

	INC280 300 mg BID	INC280 400 mg BID
Number of Participants Analyzed [units: participants]	7	24
Maximum Observed Plasma Concentration (Cmax) for INC280 at Cycle 1 Days 1 and 7 (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)		

C1D1 (n= 7, 24)	1110 (66.9%)	2580 (49.8%)
C1D7 (n= 6, 23)	1550 (22.6%)	3050 (39.5%)

Maximum Observed Plasma Concentration (Cmax) for metabolite CMN288 at Cycle 1 Days 1 and 7

	INC280 300 mg BID	INC280 400 mg BID
Number of Participants Analyzed [units: participants]	7	24
Maximum Observed Plasma Concentration (Cmax) for metabolite CMN288 at Cycle 1 Days 1 and 7 (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)		
C1D1 (n= 7, 24)	475 (27.8%)	671 (90.5%)
C1D7 (n= 6, 23)	492 (25.6%)	625 (62.4%)

Time to Reach the Maximum Plasma Concentration (Tmax) for INC280 at Cycle 1 Days 1 and 7

	INC280 300 mg BID	INC280 400 mg BID
Number of Participants Analyzed [units: participants]	7	24
Time to Reach the Maximum Plasma Concentration (Tmax) for INC280 at Cycle 1 Days 1 and 7 (units: hour) Median (Full Range)		
C1D1 (n= 7, 24)	5.60 (1.87 to 8.00)	4.01 (0.5 to 8.17)
C1D7 (n= 6, 23)	4.04 (1.17 to 6.12)	4.00 (1.07 to 8.28)

Time to Reach the Maximum Plasma Concentration (Tmax) for metabolite CMN288 at Cycle 1 Days 1 and 7

	INC280 300 mg BID	INC280 400 mg BID
Number of Participants Analyzed [units: participants]	7	24
Time to Reach the Maximum Plasma Concentration (Tmax) for metabolite CMN288 at Cycle 1 Days 1 and 7 (units: hour) Median (Full Range)		
C1D1 (n= 7, 24)	5.60 (3.92 to 8.00)	4.08 (2.00 to 8.17)
C1D7 (n= 6, 23)	5.04 (2.17 to 8.02)	4.00 (1.95 to 8.28)

Secondary Outcome Result(s)

Not Applicable

Summary of Safety

Safety Results

All-Cause Mortality

	INC280 300mg BID N = 8	INC280 400mg BID N = 27	All patients N = 35
Total participants affected	2 (25.00%)	3 (11.11%)	5 (14.29%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events were collected for the maximum duration of participants' treatment exposure plus any follow up period, approximately 36 months.
Source Vocabulary for Table Default	MedDRA 21.0
Assessment Type for Table Default	Systematic Assessment

	INC280 300mg BID N = 8	INC280 400mg BID N = 27	All patients N = 35
Total participants affected	3 (37.50%)	10 (37.04%)	13 (37.14%)
Cardiac disorders			
Myocardial infarction	0 (0.00%)	1 (3.70%)	1 (2.86%)
Pericardial effusion	0 (0.00%)	1 (3.70%)	1 (2.86%)
Gastrointestinal disorders			
Abdominal pain	0 (0.00%)	2 (7.41%)	2 (5.71%)
Upper gastrointestinal haemorrhage	0 (0.00%)	1 (3.70%)	1 (2.86%)
Vomiting	0 (0.00%)	1 (3.70%)	1 (2.86%)
General disorders and administration site conditions			
General physical health deterioration	1 (12.50%)	1 (3.70%)	2 (5.71%)
Oedema peripheral	1 (12.50%)	0 (0.00%)	1 (2.86%)
Immune system disorders			

Hypersensitivity	0 (0.00%)	1 (3.70%)	1 (2.86%)
Infections and infestations			
Escherichia infection	0 (0.00%)	1 (3.70%)	1 (2.86%)
Infection	0 (0.00%)	1 (3.70%)	1 (2.86%)
Lung infection	1 (12.50%)	0 (0.00%)	1 (2.86%)
Sepsis	0 (0.00%)	1 (3.70%)	1 (2.86%)
Metabolism and nutrition disorders			
Hypocalcaemia	0 (0.00%)	1 (3.70%)	1 (2.86%)
Hypokalaemia	0 (0.00%)	1 (3.70%)	1 (2.86%)
Hypoproteinaemia	0 (0.00%)	1 (3.70%)	1 (2.86%)
Musculoskeletal and connective tissue disorders			
Fracture pain	1 (12.50%)	0 (0.00%)	1 (2.86%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intracranial tumour haemorrhage	0 (0.00%)	1 (3.70%)	1 (2.86%)
Psychiatric disorders			
Depression	0 (0.00%)	1 (3.70%)	1 (2.86%)
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	0 (0.00%)	2 (7.41%)	2 (5.71%)
Lung infiltration	1 (12.50%)	0 (0.00%)	1 (2.86%)

Pleural effusion	1 (12.50%)	0 (0.00%)	1 (2.86%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Events were collected for the maximum duration of participants' treatment exposure plus any follow up period, approximately 36 months.
Source Vocabulary for Table Default	MedDRA 21.0
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	INC280 300mg BID N = 8	INC280 400mg BID N = 27	All patients N = 35
Total participants affected	8 (100.00%)	21 (77.78%)	29 (82.86%)
Blood and lymphatic system disorders			
Anaemia	0 (0.00%)	2 (7.41%)	2 (5.71%)
Cardiac disorders			
Palpitations	1 (12.50%)	0 (0.00%)	1 (2.86%)
Eye disorders			
Lacrimation increased	1 (12.50%)	0 (0.00%)	1 (2.86%)
Gastrointestinal disorders			
Abdominal pain	0 (0.00%)	2 (7.41%)	2 (5.71%)
Constipation	0 (0.00%)	4 (14.81%)	4 (11.43%)

Diarrhoea	0 (0.00%)	5 (18.52%)	5 (14.29%)
Nausea	3 (37.50%)	11 (40.74%)	14 (40.00%)
Vomiting	1 (12.50%)	4 (14.81%)	5 (14.29%)
General disorders and administration site conditions			
Chills	0 (0.00%)	2 (7.41%)	2 (5.71%)
Fatigue	5 (62.50%)	11 (40.74%)	16 (45.71%)
Mucosal inflammation	0 (0.00%)	2 (7.41%)	2 (5.71%)
Oedema peripheral	3 (37.50%)	6 (22.22%)	9 (25.71%)
Pain	1 (12.50%)	1 (3.70%)	2 (5.71%)
Peripheral swelling	1 (12.50%)	1 (3.70%)	2 (5.71%)
Pyrexia	0 (0.00%)	3 (11.11%)	3 (8.57%)
Infections and infestations			
Fungal skin infection	1 (12.50%)	0 (0.00%)	1 (2.86%)
Lung infection	1 (12.50%)	0 (0.00%)	1 (2.86%)
Nasopharyngitis	1 (12.50%)	1 (3.70%)	2 (5.71%)
Respiratory tract infection	0 (0.00%)	2 (7.41%)	2 (5.71%)
Upper respiratory tract infection	0 (0.00%)	2 (7.41%)	2 (5.71%)
Injury, poisoning and procedural complications			
Ligament sprain	1 (12.50%)	0 (0.00%)	1 (2.86%)
Investigations			

Alanine aminotransferase increased	0 (0.00%)	3 (11.11%)	3 (8.57%)
Aspartate aminotransferase increased	0 (0.00%)	2 (7.41%)	2 (5.71%)
Blood creatine phosphokinase increased	1 (12.50%)	0 (0.00%)	1 (2.86%)
Blood creatinine increased	1 (12.50%)	2 (7.41%)	3 (8.57%)
Metabolism and nutrition disorders			
Decreased appetite	1 (12.50%)	5 (18.52%)	6 (17.14%)
Hypoalbuminaemia	0 (0.00%)	2 (7.41%)	2 (5.71%)
Hypocalcaemia	0 (0.00%)	2 (7.41%)	2 (5.71%)
Hypokalaemia	1 (12.50%)	0 (0.00%)	1 (2.86%)
Hypomagnesaemia	0 (0.00%)	2 (7.41%)	2 (5.71%)
Hypophosphataemia	1 (12.50%)	0 (0.00%)	1 (2.86%)
Musculoskeletal and connective tissue disorders			
Arthralgia	0 (0.00%)	3 (11.11%)	3 (8.57%)
Back pain	1 (12.50%)	0 (0.00%)	1 (2.86%)
Fracture pain	1 (12.50%)	0 (0.00%)	1 (2.86%)
Intervertebral disc protrusion	1 (12.50%)	0 (0.00%)	1 (2.86%)
Muscle spasms	1 (12.50%)	2 (7.41%)	3 (8.57%)
Muscular weakness	1 (12.50%)	0 (0.00%)	1 (2.86%)
Myalgia	1 (12.50%)	0 (0.00%)	1 (2.86%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain	1 (12.50%)	1 (3.70%)	2 (5.71%)
Nervous system disorders			
Brain oedema	1 (12.50%)	0 (0.00%)	1 (2.86%)
Dizziness	2 (25.00%)	0 (0.00%)	2 (5.71%)
Headache	1 (12.50%)	3 (11.11%)	4 (11.43%)
Seizure	1 (12.50%)	0 (0.00%)	1 (2.86%)
Somnolence	2 (25.00%)	0 (0.00%)	2 (5.71%)
Psychiatric disorders			
Anxiety	0 (0.00%)	2 (7.41%)	2 (5.71%)
Depression	1 (12.50%)	2 (7.41%)	3 (8.57%)
Reproductive system and breast disorders			
Vaginal discharge	1 (12.50%)	0 (0.00%)	1 (2.86%)
Respiratory, thoracic and mediastinal disorders			
Cough	0 (0.00%)	3 (11.11%)	3 (8.57%)
Dyspnoea	2 (25.00%)	4 (14.81%)	6 (17.14%)
Lung infiltration	1 (12.50%)	0 (0.00%)	1 (2.86%)
Skin and subcutaneous tissue disorders			
Pruritus	0 (0.00%)	2 (7.41%)	2 (5.71%)
Rash	1 (12.50%)	4 (14.81%)	5 (14.29%)

Vascular disorders			
Flushing	1 (12.50%)	0 (0.00%)	1 (2.86%)
Hypotension	0 (0.00%)	2 (7.41%)	2 (5.71%)
Orthostatic hypotension	1 (12.50%)	0 (0.00%)	1 (2.86%)

Other Relevant Findings

Although one subject met the criteria for drug-induced liver injury (DILI) at end of treatment (EOT), it was unrelated to the study treatment and this subject discontinued due to disease progression with new metastatic lesions in the liver. No other clinically significant hematology or clinical chemistry abnormalities were observed. No clinically significant ECG and vital signs changes were observed.

Conclusion:

There were no occurrences of DLTs on the study. When administered with food, an increase in capmatinib and CMN288 exposure was observed with dose increase from 300 mg bid to 400 mg bid. Based on the review of all safety and PK data, capmatinib was well tolerated when administered with food in subjects with MET-dysregulated advanced solid tumors. Overall, safety observations were in line with the existing safety profile for capmatinib with no major or new safety observations.

Date of Clinical Trial Report

05-Dec-2018