Clinical trial results:
An open label, multi-center nilotinib roll-over protocol for patients who have completed a previous Novartis sponsored nilotinib study and are judged by the investigator to benefit from continued nilotinib treatment

Summary

EudraCT number	2012-003902-28
Trial protocol	AT IT ES HU NL GB SK SE FR
Global end of trial date	07 July 2023

Results information

Result version number	v2 (current)
This version publication date	01 February 2024
First version publication date	04 January 2024
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CAMN107A2409

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01735955
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 July 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective - To evaluate long-term safety data (Serious Adverse Events (SAEs) and Adverse Events (AEs))
Secondary objective - To evaluate clinical benefit as assessed by the investigator

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 March 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	Singapore: 11
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	57
EEA total number of subjects	21

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	4
Adolescents (12-17 years)	3
Adults (18-64 years)	30
From 65 to 84 years	19
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study had no screening period. 57 patients were enrolled and treated with nilotinib in this study. Pts were rolled over from 5 parent studies with the following indications: Chronic myelogenous leukemia (CML), Metastatic gastrointestinal stromal tumors (GIST), Acute lymphoblastic leukemia (ALL) & Receptor tyrosine kinase (KIT) mutated melanoma.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Nilotinib

Arm description:

Adult patients: ≤ 800mg/day; Pediatric patients: 230mg/m2 twice daily (BID) and ≤ 800mg/day

Arm type	Experimental
Investigational medicinal product name	nilotinib
Investigational medicinal product code	AMN107
Other name	Tasigna
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Adult patients: ≤ 800mg/day; Pediatric patients: 230mg/m2 twice daily (BID) and ≤ 800mg/day

Number of subjects in period 1	Nilotinib
Started	57
Completed	20
Not completed	37
Patient withdrew consent	2
Physician decision	4
Disease progression	24
Adverse event, non-fatal	5
Administrative problems	1
Patient/guardian decision	1

Baseline characteristics

Reporting groups	
Reporting group title	Nilotinib
Reporting group description:	
Adult patients: ≤ 800mg/day; Pediatric patients: 230mg/m2 twice daily (BID) and ≤ 800mg/day	

Reporting group values	Nilotinib	Total	
Number of subjects	57	57	
Age Categorical Units: Participants			
<=18 years	7	7	
Between 18 and 65 years	30	30	
>=65 years	20	20	
Age Continuous Units: years			
arithmetic mean	53.02		
standard deviation	± 19.278	-	
Sex: Female, Male Units: Participants			
Female	30	30	
Male	27	27	

End points

End points reporting groups

Reporting group title	Nilotinib

Reporting group description:

Adult patients: ≤ 800mg/day; Pediatric patients: 230mg/m2 twice daily (BID) and ≤ 800mg/day

Primary: Number of participants with adverse events and serious adverse events

End point title	Number of participants with adverse events and serious adverse events[1]

End point description:

An Adverse Event (AE) is any untoward medical occurrence (eg any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

Serious adverse event (SAE) case data were collected in the Safety Database. Adverse event (AE) data (both non-serious and serious) were collected in the Clinical database.

Max. = Maximum
Yrs = Years
Approx. = Approximately
eCRF = electronic Case Report Form
Time = timeframe

End point type	Primary

End point timeframe:

SAE case data were collected the entire study duration after first dose of study treatment up to a max. time of approx. 10 yrs. AEs (both non-serious and serious) were collected in the eCRF 3 yrs after study initiation up to a max. time of approx. 7 yrs.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: NA for a single arm study and NA for AE data.

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Participants				
Adverse Events - total	29			
Adverse Events - Treatment-related adverse events	15			
SAEs - total	17			
SAEs - Treatment-related SAEs	2			
AEs leading to discontinuation - total	3			
Treatment-related AEs leading to discontinuation	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinical benefit from nilotinib

End point title	Number of participants with clinical benefit from nilotinib

End point description:

Number of patients (pts) with clinical benefit as assessed by investigator.

Clinical benefit data were first collected 3 years after study initiation and up to a maximum timeframe of approx. 7 years & 3 months at a patient level (up to Week 528 total at the study level).

Pts who discontinued in the first 3 years after study initiation didn't have any clinical benefit data collected. Pts who enrolled in the first 3 years after study initiation only had clinical benefit data collected starting at approx. the third year of the study until the end of the patient's participation in the study. Pts who enrolled after the first 3 years after study initiation had all clinical benefit data collected until the end of the patient's participation in the study.

Data for the earlier time points are provided only for later enrolled pts. Data for the later time points are provided only for the earlier enrolled pts.

The time point per patient was calculated from the date of first drug intake.

End point type	Secondary

End point timeframe:

Clinical benefit data were first collected 3 years after study initiation and are reported at baseline, Weeks 24, 48, 72, 96, 144, 192, 240, 288, 336, 384, 432, 480, and 528.

End point values	Nilotinib			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Participants				
Patients with clinical benefit - Baseline	15			
Patients with clinical benefit - Week 24	11			
Patients with clinical benefit - Week 48	17			
Patients with clinical benefit - Week 72	11			
Patients with clinical benefit - Week 96	19			
Patients with clinical benefit - Week144	23			
Patients with clinical benefit - Week 192	26			
Patients with clinical benefit - Week 240	20			
Patients with clinical benefit - Week 288	9			
Patients with clinical benefit - Week 336	9			
Patients with clinical benefit - Week 384	7			
Patients with clinical benefit - Week 432	6			
Patients with clinical benefit - Week 480	6			
Patients with clinical benefit - Week 528	4			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAE case data were collected the entire study duration after first dose of study treatment up to a max. time of approx. 10 yrs. AEs (both non-serious and serious) were collected in the eCRF 3 yrs after study initiation up to a max. time of approx. 7 yrs.

Adverse event reporting additional description:

Serious adverse event (SAE) case data were collected in the Safety Database. Adverse event (AE) data (both non-serious and serious) were collected in the Clinical database.

Max. = Maximum
Yrs = Years
Approx. = Approximately
eCRF = electronic Case Report Form
Time = timeframe

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Nilotinib

Reporting group description:

Adult patients: ≤ 800mg/day; Pediatric patients: 230mg/m2 twice daily (BID) and ≤ 800mg/day

Serious adverse events	Nilotinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 57 (29.82%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastrointestinal stromal tumour			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral arterial occlusive disease			

subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral artery occlusion			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Small intestinal resection			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Ischaemic stroke			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Hydronephrosis			

subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal osteoarthritis			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dengue fever			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pyelonephritis acute			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Nilotinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 57 (35.09%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	5		
Paraesthesia			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	4		
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 4		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 4		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 4		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 4 3 / 57 (5.26%) 3		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 4 3 / 57 (5.26%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 September 2013	Added monthly pregnancy tests for female patients of childbearing potential to reflect the requirement of highly effective contraception for patients on nilotinib treatment. Clarified that dose modifications were based on guidelines provided in the parent protocol, as well as investigator's judgment. Clarified that patients could have access to the same strengths as specified in the parent protocol. Clarified that patients who were pregnant, who withdrew consent or died were required to be withdrawn from the study.
24 June 2014	Incorporated guidance for the management of serum cholesterol and blood glucose increases, other cardiac risk factors, and ischemic vascular or ischemic cardiovascular events occurring in patients treated with nilotinib. Updated the exclusion criteria relating to male trial participant's use highly effective contraception to be aligned with the current Investigator Brochure.
07 April 2016	Included the collection of all AEs (including non-serious and serious AEs) and an investigator attestation of continued clinical benefit into the clinical database. Increased visit frequency from annually to quarterly. Included hepatitis B virus testing as one of the study procedures to identify study patients who might have been at risk of hepatitis B reactivation. Included collection of relevant medical history/current medical condition. Included the study evaluation completion eCRF page.
27 July 2016	Corrected an error in the language regarding pregnancy outcome collection. Pregnancy outcomes from female partners of any males who took study treatment was not collected in this study as nilotinib is not genotoxic and no effects on sperm count, motility, or on fertility were noted in animal studies.
30 August 2018	Provided further clarity to the end of study definition and trial timelines

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported