Clinical trial results:
Phase III Trial Evaluating the Effectiveness of a Dose Adjustment of Imatinib Mesylate on the Molecular Response (MIM)

Summary

EudraCT number	2008-007094-20
Trial protocol	FR
Global end of trial date	01 January 2017

Results information

Result version number	v1 (current)
This version publication date	20 January 2022
First version publication date	20 January 2022

Trial information

Trial identification

Sponsor protocol code	IB 2009-07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01827930
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut Bergonié
Sponsor organisation address	229 cours de l'Argonne, Bordeaux, France, 33076
Public contact	Regulatory Affairs Management Desk, Institut Bergonié, drci@bordeaux.unicancer.fr
Scientific contact	Regulatory Affairs Management Desk, Institut Bergonié, drci@bordeaux.unicancer.fr

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 January 2017
Global end of trial reached?	Yes
Global end of trial date	01 January 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase III Trial to Evaluate the Effectiveness of a Dose Adjustment of Imatinib Mesylate on the Molecular Response in Patients With chronic myeloid leukemia (CML) in Chronic Phase Treated With IM 400 mg / Day for at Least Two Years, Complete Cytogenetic Response for at Least One Year

Protection of trial subjects:

A supervisory committee is constitued to evaluate the benefit/risk ratio along the study period.

Background therapy:

The Imatinib Mesylate at a dose of 400 mg / day is the standard treatment for patients with CML-CP. Recent studies show that the quality of response rate (complete cytogenetic response and major molecular response rate) is dependent on the residual plasma Imatinib.

Evidence for comparator:

The Imatinib Mesylate at a dose of 400 mg / day is the standard treatment for patients with CML-CP. Recent studies show that the quality of response rate (complete cytogenetic response and major molecular response rate) is dependent on the residual plasma Imatinib. This study aims to evaluate the effectiveness of a strategy for dose adjustment of Imatinib Mesylate based on the measurement of the residual plasma imatinib in patients treated for at least 2 years Imatinib 400 mg / d in complete cytogenetic response for at least 1 year.

Actual start date of recruitment	14 December 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 68
Worldwide total number of subjects	68
EEA total number of subjects	68

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	65
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Criteria
Inclusion Criteria:

Patients with CML-CP treated for at least two years by Imatinib Mesylate 400 mg / d,
Patients in complete cytogenetic response for at least 1 year
Patients with residual disease detectable by quantitative RT-PCR (RQ-PCR)
ECOG ≤ 2,
Age ≥ 18 years
Signed informed consent,
Membership of a social security system

Period 1

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

Blinding implementation details:

not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Randomized trial / Control Arm: Imatinib 400

Arm description:

Patients with IM concentration < 1000ng/mL are randomized between :
(1) Experimental Arm : adapted strategy (up to 600 MG IM)
(2) Control Arm : standard strategy (400 MG IM)

Arm type	Active comparator
Investigational medicinal product name	Imatinib Mesylate
Investigational medicinal product code	
Other name	Glivec
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Drug: Imatinib Mesylate 600 MG Oral Tablet

Arm title	Randomized trial / Experimental Arm: Imatinib 600

Arm description:

Patients with IM concentration < 1000ng/mL are randomized between :
(1) Experimental Arm : adapted strategy (up to 600 MG IM)
(2) Control Arm : standard strategy (400 MG IM)

Arm type	Experimental
Investigational medicinal product name	Imatinib Mesylate
Investigational medicinal product code	
Other name	Glivec
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Imatinib Mesylate 600 MG Oral Tablet:

Arm title	Parallel cohort: Imatinib 400

Arm description:

Patients with IM concentration > 1000ng/mL are included in a parallel cohort and receive standard strategy (400 MG IM)

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Randomized trial / Control Arm: Imatinib 400	Randomized trial / Experimental Arm: Imatinib 600	Parallel cohort: Imatinib 400
Started	25	24	19
Completed	25	24	19

Baseline characteristics

Reporting groups	
Reporting group title	Randomized trial / Control Arm: Imatinib 400
Reporting group description:	
Patients with IM concentration < 1000ng/mL are randomized between : (1) Experimental Arm : adapted strategy (up to 600 MG IM) (2) Control Arm : standard strategy (400 MG IM)	
Reporting group title	Randomized trial / Experimental Arm: Imatinib 600
Reporting group description:	
Patients with IM concentration < 1000ng/mL are randomized between : (1) Experimental Arm : adapted strategy (up to 600 MG IM) (2) Control Arm : standard strategy (400 MG IM)	
Reporting group title	Parallel cohort: Imatinib 400
Reporting group description:	
Patients with IM concentration > 1000ng/mL are included in a parallel cohort and receive standard strategy (400 MG IM)	

Reporting group values	Randomized trial / Control Arm: Imatinib 400	Randomized trial / Experimental Arm: Imatinib 600	Parallel cohort: Imatinib 400
Number of subjects	25	24	19
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	52.7	50.6	65.3
full range (min-max)	25.1 to 79.1	27.2 to 72.0	34.3 to 80.4
Gender categorical Units: Subjects			
Female	6	4	6
Male	19	20	13

Reporting group values	Total		
Number of subjects	68		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		

Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	16		
Male	52		

End points

End points reporting groups

Reporting group title	Randomized trial / Control Arm: Imatinib 400
Reporting group description:	
Patients with IM concentration < 1000ng/mL are randomized between : (1) Experimental Arm : adapted strategy (up to 600 MG IM) (2) Control Arm : standard strategy (400 MG IM)	
Reporting group title	Randomized trial / Experimental Arm: Imatinib 600
Reporting group description:	
Patients with IM concentration < 1000ng/mL are randomized between : (1) Experimental Arm : adapted strategy (up to 600 MG IM) (2) Control Arm : standard strategy (400 MG IM)	
Reporting group title	Parallel cohort: Imatinib 400
Reporting group description:	
Patients with IM concentration > 1000ng/mL are included in a parallel cohort and receive standard strategy (400 MG IM)	

Primary: Percentage of Patients Presenting a Decline of the BCR-ABL Transcript Rate at 12 Months From Baseline

End point title	Percentage of Patients Presenting a Decline of the BCR-ABL Transcript Rate at 12 Months From Baseline
End point description:	
The BCR-ABL transcript rate was analysed by molecular biology by RQ-PCR at study entry, 3 months, 6 months, 9 months and 12 months. Treatment is considered effective at 12 months if: for patients with an inclusion transcript rate less than 0.1%: the transcript rate at 12 months is less or equal to 0.001% or undetectable. for patients with an inclusion transcript rate greater than 0.1% : the transcript rate at 12 months is less or equal to 0.1% or undetectable. If BCR-ABL transcript level was unavailable at M12, the treatment was considered ineffective.	
End point type	Primary
End point timeframe:	
12 Months From Baseline	

End point values	Randomized trial / Control Arm: Imatinib 400	Randomized trial / Experimental Arm: Imatinib 600	Parallel cohort: Imatinib 400	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	24	19	
Units: subjects	8	7	2	

Statistical analyses

Statistical analysis title	Statistical analysis for primary outcome

Statistical analysis description:

The proportion of Patients Presenting a Decline of the BCR-ABL Transcript Rate at 12 Months From Baseline was estimated as the number of patients with a Decline of the BCR-ABL Transcript Rate at 12 Months From Baseline divided by the number of all patients. The 95% confidence interval is reported (binomial law)

Comparison groups	Randomized trial / Experimental Arm: Imatinib 600 v Randomized trial / Control Arm: Imatinib 400
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.05 [2]
Method	t-test, 2-sided
Parameter estimate	Odds ratio (OR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	3.86
Variability estimate	Standard error of the mean

Notes:

[1] - Rates are reported for each arm. no comparison was performed.

[2] - not applicable.

Secondary: Molecular Response at 12 Months

End point title	Molecular Response at 12 Months

End point description:

The molecular response is defined by the measurement of BCR-ABL transcript rate by quantitative RT-PCR (RQ-PCR) on peripheral venous blood according to international standards.

It is defined as:
- Major Molecular Response (MMR): BRC-ABL transcript rate ≤ 0.1%
- Complete Molecular Response (CMR): transcript BCR-ABL undetectable and non quantifiable.

End point type	Secondary

End point timeframe:

12 months from baseline

End point values	Randomized trial / Control Arm: Imatinib 400	Randomized trial / Experimental Arm: Imatinib 600	Parallel cohort: Imatinib 400	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	24	19	
Units: Subjects	19	20	12	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

throughout the follow-up of the patient, up to 1 year

Adverse event reporting additional description:

All adverse envent (related and unrelated to treatment) were reported.

All serious adverse envent (related and unrelated to treatment) were reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	2

Reporting groups

Reporting group title	Randomized trial / Control Arm: Imatinib 400

Reporting group description:

Patients with IM concentration < 1000ng/mL are randomized between :
(1) Experimental Arm : adapted strategy (up to 600 MG IM)
(2) Control Arm : standard strategy (400 MG IM)

Reporting group title	Randomized trial / Experimental Arm: Imatinib 600

Reporting group description:

Patients with IM concentration < 1000ng/mL are randomized between :
(1) Experimental Arm : adapted strategy (up to 600 MG IM)
(2) Control Arm : standard strategy (400 MG IM)

Reporting group title	Parallel cohort: Imatinib 400

Reporting group description:

Patients with IM concentration > 1000ng/mL are included in a parallel cohort and receive standard strategy (400 MG IM)

Serious adverse events	Randomized trial / Control Arm: Imatinib 400	Randomized trial / Experimental Arm: Imatinib 600	Parallel cohort: Imatinib 400
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 25 (16.00%)	3 / 24 (12.50%)	0 / 19 (0.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastrointestinal - Other			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal/Genitourinary - Other			

subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac General - Other (Specify, __)			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac ischemia/infarction			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal/Soft Tissue - Other			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary/Upper Respiratory - Other			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Infections and infestations			
Infection - Other			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Randomized trial / Control Arm: Imatinib 400	Randomized trial / Experimental Arm: Imatinib 600	Parallel cohort: Imatinib 400
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 25 (48.00%)	24 / 24 (100.00%)	15 / 19 (78.95%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 25 (8.00%)	1 / 24 (4.17%)	1 / 19 (5.26%)
occurrences (all)	2	1	1
Carotid			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue (asthenia, lethargy, malaise)			
subjects affected / exposed	3 / 25 (12.00%)	9 / 24 (37.50%)	2 / 19 (10.53%)
occurrences (all)	4	10	2
Edema:head and neck			
subjects affected / exposed	0 / 25 (0.00%)	3 / 24 (12.50%)	1 / 19 (5.26%)
occurrences (all)	0	6	1
Edema:limb			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Lymphatics - Other			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Immune system disorders			
Allergic reaction/hypersensitivity (including drug fever)			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	2
Nose			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	1 / 19 (5.26%)
occurrences (all)	0	1	1

Cough			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	2 / 19 (10.53%)
occurrences (all)	0	1	2
Dyspnea (shortness of breath)			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	1 / 19 (5.26%)
occurrences (all)	0	2	1
Investigations			
Leukocytes (total WBC)			
subjects affected / exposed	1 / 25 (4.00%)	3 / 24 (12.50%)	1 / 19 (5.26%)
occurrences (all)	3	3	2
Lymphopenia			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	1 / 19 (5.26%)
occurrences (all)	3	1	1
Neutrophils/granulocytes (ANC/AGC)			
subjects affected / exposed	1 / 25 (4.00%)	4 / 24 (16.67%)	1 / 19 (5.26%)
occurrences (all)	2	4	1
Cardiac disorders			
Cardiac General - Other			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Nervous system disorders			
Head/headache			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	2 / 19 (10.53%)
occurrences (all)	1	1	2
Blood and lymphatic system disorders			
Hemoglobin			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	2 / 19 (10.53%)
occurrences (all)	0	2	2
Eye disorders			

Cataract			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Ocular/Visual - Other			
subjects affected / exposed	2 / 25 (8.00%)	2 / 24 (8.33%)	2 / 19 (10.53%)
occurrences (all)	2	2	2
Watery eye (epiphora, tearing) † 1 [3]			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	0 / 25 (0.00%)	6 / 24 (25.00%)	4 / 19 (21.05%)
occurrences (all)	0	7	4
Dry mouth/salivary gland (xerostomia)			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Gastrointestinal - Other			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	1 / 19 (5.26%)
occurrences (all)	0	7	1
Stomach			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	1 / 19 (5.26%)
occurrences (all)	0	2	1
Skin and subcutaneous tissue disorders			
Dermatology/Skin - Other			
subjects affected / exposed	1 / 25 (4.00%)	3 / 24 (12.50%)	1 / 19 (5.26%)
occurrences (all)	1	4	1
Induration/fibrosis (skin and subcutaneous tissue)			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pruritus/itching			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	1 / 19 (5.26%)
occurrences (all)	0	2	1
Renal and urinary disorders			
Renal failure			

subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Renal/Genitourinary - Other			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal/Soft Tissue - Other			
subjects affected / exposed	3 / 25 (12.00%)	9 / 24 (37.50%)	2 / 19 (10.53%)
occurrences (all)	4	12	2
Joint			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	2 / 19 (10.53%)
occurrences (all)	0	1	2
Infections and infestations			
Infection - Other			
subjects affected / exposed	2 / 25 (8.00%)	6 / 24 (25.00%)	4 / 19 (21.05%)
occurrences (all)	2	8	5
Metabolism and nutrition disorders			
Phosphate, serum-low (hypophosphatemia)			
subjects affected / exposed	1 / 25 (4.00%)	2 / 24 (8.33%)	1 / 19 (5.26%)
occurrences (all)	1	2	1
Triglyceride, serum-high (hypertriglyceridemia)			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2009	Protocol V2.1 dated 22-sep-2009
18 June 2012	Protocol V3 dated 02-jan-2012
16 May 2014	Protocol V4 dated 28-feb-2014
30 August 2016	Protocol V6 dated 06-jul-2016

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported