Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Nilotinib

Trial Indication(s)

Newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase

Protocol Number

CAMN107ECN02

Protocol Title

ENESTChina: A phase III multi-center, open-label, randomized study of nilotinib versus imatinib in Chinese adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP)

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase 3

Study Start/End Dates

Study Start Date: April 2011 (Actual)
Study Completion Date: October 2014 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a Phase III, open-label, multicenter, randomized study of nilotinib 300 mg bid versus imatinib 400 mg qd, which was conducted in China. The study was designed to determine whether the treatment of ethnically Chinese patients with newly diagnosed, previously untreated Ph+ CML-CP with nilotinib 300 mg bid demonstrated improved efficacy compared to imatinib 400 mg qd.

The primary efficacy endpoint was the rate of major molecular response (MMR), defined as a BCR-ABL ratio of ≤ 0.1% measured by real-time quantitative PCR (RQ-PCR) at 12 months after the start of first study medication.

Centers

China(14)

Objectives:

Primary objectives

The primary objective was to compare the efficacy (major molecular response (MMR) rate at 12 months) of nilotinib at 300 mg bid with that of imatinib 400 mg qd in patients with newly diagnosed previously untreated Ph+ CML-CP. Data for the primary objective was presented in the 12 month clinical study report.

Secondary objectives

To compare:

- Rate of MMR at and by scheduled time points
- Time to MMR
- Rate of durable MMR at 24 months

- Duration of MMR
- Rate of complete cytogenetic response (CCyR) at and by scheduled time points
- Time to CCyR
- Duration of CCyR
- Time to progression to accelerated phase (AP)/blast crisis (BC)
- Progression-free survival (PFS)
- Event-free survival (EFS)
- Overall survival (OS)
- Rate of complete hematologic response (CHR) by scheduled time points
- Rates of suboptimal response and treatment failure

To evaluate:

- The safety profile of nilotinib and imatinib in patients with newly diagnosed, previously untreated Ph+ CML-CP
- The actual dose-intensity delivered in each treatment arm
- The pharmacokinetics/pharmacodynamics of nilotinib and imatinib in patients with newly diagnosed, previously untreated Ph+ CML-CP

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

Test product: Nilotinib was labeled as AMN107 and supplied by Novartis as 150 mg and 200 mg hard gelatin capsules and administered orally at 300 mg bid.

Reference therapy: Imatinib was labeled as STI571 and supplied by Novartis as 100 mg tablets, administered orally at 400 or 600 mg qd, depending on the dose.

Statistical Methods

Efficacy was analyzed using the full analysis set (FAS) and included all randomized patients according to the treatment they were randomized to (intent-to-treat principle). Safety was analyzed for all patients who received at least one dose of study medication according to the medication actually received.

The primary objective was to compare the MMR rate at 12 months in the nilotinib 300 mg bid arm to that of the imatinib 400 mg qd arm. The primary efficacy variable was analyzed and reported in the 12-month clinical study report.

The analysis of the secondary efficacy endpoints reported here was based on the FAS. The comparison performed was nilotinib 300 mg bid versus imatinib 400 mg qd. P-values for this comparison for all secondary efficacy endpoints reported are provided for descriptive purposes and were not adjusted for multiple comparisons as per protocol. Therefore, these should be considered as nominal p-values without the reference threshold for statistical significance.

Response rates ‘at’ and ‘by’ scheduled time points were presented with 95% exact Pearson-Clopper CI by treatment group. In addition, the 95% CI for the difference in response rates between treatment groups was provided using the Wald method. In the analysis ‘by’ scheduled time points, patients who had achieved a response at or before the time point were displayed as responder, no matter if they lost the response/discontinued or not. Therefore, this response rate represented the best observed response rate up to that specific time point. The response rates were compared between treatment groups using the CMH test stratified by Sokal risk group and by prior IFN therapy.

Time to response, duration of response, time to progression to AP/BC, PFS, EFS, and OS analyses were performed using the Kaplan-Meier method. These variables (except duration of response) were compared between treatment groups using a log-rank test stratified by Sokal risk group and prior IFN therapy. The hazard ratio and 95% CI for these variables were derived from a Cox model stratified by Sokal risk group and prior IFN therapy.

All the safety analyses were based on the safety set and summarized overall and by safety treatment group. AE groups of special interest were summarized separately.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Patients of Chinese ethnicity greater than or equal to 18 years of age
- ECOG 0, 1, or 2.
- Patients with CML-CP (Ph+) within 6 months of diagnosis (date of initial diagnosis is the date of first cytogenetic analysis). Standard conventional cytogenetic analysis must be done on bone marrow. (FISH cannot be used)
- Diagnosis of chronic myelogenous leukemia in chronic phase with cytogenetic confirmation for the presence of Philadelphia

chromosome of (9;22 translocation; less than 20 metaphases may be used for diagnosis
• Documented chronic phase CML will meet all the criteria defined by:
o < 15% blasts in peripheral blood and bone marrow
o < 30% blasts plus promyelocytes in peripheral blood and bone marrow
o < 20% basophils in the peripheral blood
o ≥ 100 x 109/L (≥ 100,000/mm3) platelets
• No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly
• Adequate organ function as defined by:
o Total bilirubin < 1.5 x ULN
o SGOT and SGPT < 2.5 x ULN
o Creatinine < 1.5 x ULN
o Serum amylase and lipase ≤ 1.5 x ULN
o Alkaline phosphatase ≤ 2.5 x ULN unless considered tumor related.
• Patients must have the following laboratory values (≥ LLN (lower limit of normal) or corrected to within normal limits with supplements prior to the first dose of study medication.):
o Potassium ≥ LLN
o Magnesium ≥ LLN
o Phosphate ≥ LLN
o Total calcium (corrected for serum albumin) ≥ LLN.
• Ability to provide written informed consent prior to any study related screening procedures being performed.

Exclusion Criteria:
• Patients with previously documented T315I mutations;
• Treatment with tyrosine kinase inhibitor(s) prior to study entry is not allowed, except in the following situation: in emergent cases where the patient requires disease management while awaiting study start, commercial supplies of Gleevec/Glivec at any dose may be prescribed to the patient but for no longer than 2 weeks in duration.
• Treatment with IFN for more than 3 months.
• Impaired cardiac function including any one of the following:
• Complete left bundle branch block
• Long QT syndrome or a known family history of long QT syndrome.
• History of or presence of clinically significant ventricular or atrial tachyarrhythmias
• Clinically significant resting bradycardia (<50 beats per minute)
• QTc > 450 msec If QTcF >450 msec and electrolytes are not within normal ranges, electrolytes should be corrected and then the patient re-screened for QTc
• History of clinically documented myocardial infarction within past 12 months

• History of unstable angina (during the last 12 months)
• Other clinically significant heart disease (e.g., congestive heart failure or uncontrolled hypertension).
• Known cytopathologically confirmed CNS infiltration (in absence of suspicion of CNS involvement, lumbar puncture not required).
• Severe or uncontrolled medical conditions (i.e. uncontrolled diabetes, active or uncontrolled infection).
• History of significant congenital or acquired bleeding disorder unrelated to cancer.
• Major surgery within 4 weeks prior to Day 1 of study or who have not recovered from prior surgery.
• Treatment with other investigational agents (defined as not used in accordance with the approved indication) within 30 days of Day 1.
• History of non-compliance to medical regimens or inability to grant consent.
• Patients with another primary malignancy except if the other primary malignancy is neither currently clinically significant or requiring active intervention
• Patients actively receiving therapy with strong CYP3A4 inhibitors (e.g., erythromycin, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir, mibefradil) and the treatment cannot be either discontinued or switched to a different medication prior to starting study drug. See link for complete list of these medications: http://medicine.iupui.edu/flockhart/table.htm or reference Protocol post text appendix 1.
• Patients actively receiving therapy with strong CYP3A4 inducers (e.g., dexamthasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbitol, St. John's Wort) and the treatment cannot be either discontinued or switched to a different medication prior to starting study drug. See link for complete list of these medications: http://medicine.iupui.edu/flockhart/table.htm or reference Protocol post text appendix 1.
• Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or gastric bypass surgery)
• History of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis.
• Acute or chronic liver, pancreatic or severe renal disease considered unrelated to disease.
• Patients who are currently receiving treatment with any medications that have the potential to prolong the QT interval and the treatment cannot be either discontinued or switched to a different medication prior to starting study drug (Please see http://www.torsades.org/medical-pros/drug-lists/printable-drug-list.cfm for a comprehensive list of agents that prolong the QT interval).
• Patients who are: (a) pregnant, (b) breast feeding, (c) of childbearing potential without a negative pregnancy test prior to baseline and (d) female of childbearing potential unwilling to use contraceptive precautions throughout the trial (post-menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential)

Other protocol-defined inclusion/exclusion criteria may apply

Participant Flow Table

Overall Study

	Imatinib	Nilotinib
Started	133	134
Intended to continue into Extension	112	113
Completed	113	113
Not Completed	20	21
Adverse Event	3	5
Withdrawal by Subject	4	5
Lost to Follow-up	1	0
Disease Progression	6	5
Protocol Violation	1	0
Suboptimal response/treatment failure	5	6

Baseline Characteristics

	Imatinib	Nilotinib	Total
Number of Participants [units: participants]	133	134	267

Age Continuous (units: Years) Mean ± Standard Deviation	39.7±12.86	41.5±12.76	40.6±12.82
Gender, Male/Female (units: Participants)			
Female	52	43	95
Male	81	91	172

Summary of Efficacy

Primary Outcome Result(s)

Major Molecular Response (MMR) at 12 months - with imputation.

	Imatinib	Nilotinib
Number of Participants Analyzed [units: participants]	133	134
Major Molecular Response (MMR) at 12 months - with imputation. (units: Percentage of Participants) Number (95% Confidence Interval)	27.8 (20.4 to 36.3)	52.2 (43.4 to 60.9)

Secondary Outcome Result(s)

MMR Rate at each time point

	Imatinib	Nilotinib
Number of Participants Analyzed [units: participants]	133	134
MMR Rate at each time point (units: Percentage of Participants) Number (95% Confidence Interval)		
3 Months	3.0 (0.8 to 7.5)	13.4 (8.2 to 20.4)
6 Months	18.0 (11.9 to 25.6)	44.8 (36.2 to 53.6)
9 Months	21.1 (14.5 to 29.0)	47.8 (39.1 to 56.6)
12 Months	27.8 (20.4 to 36.3)	53.0 (44.2 to 61.7)
15 Months	36.1 (27.9 to 44.9)	59.0 (50.1 to 67.4)
18 Months	40.6 (32.2 to 49.5)	57.5 (48.6 to 66.0)
21 Months	41.4 (32.9 to 50.2)	61.9 (53.2 to 70.2)
24 Months	49.6 (40.8 to 58.4)	61.9 (53.2 to 70.2)
36 Months	59.4 (50.5 to 67.8)	68.7 (60.1 to 76.4)
42 Months	47.4	46.3

	(38.7 to 56.2)	(37.6 to 55.1)

Best MMR by each timepoint

	Imatinib	Nilotinib
Number of Participants Analyzed [units: participants]	133	134
Best MMR by each timepoint (units: Percentage of Participants) Number (95% Confidence Interval)		
Overall	66.9 (58.2 to 74.8)	73.9 (65.6 to 81.1)
Month 3	3.0 (0.8 to 7.5)	13.4 (8.2 to 20.4)
Month 6	18.0 (11.9 to 25.6)	45.5 (36.9 to 54.3)
Month 9	22.6 (15.8 to 30.6)	51.5 (42.7 to 60.2)
Month 12	30.8 (23.1 to 39.4)	56.0 (47.1 to 64.5)
Month 15	37.6 (29.3 to 46.4)	62.7 (53.9 to 70.9)
Month 18	42.9 (34.3 to 51.7)	64.2 (55.4 to 72.3)
Month 21	46.6 (37.9 to 55.5)	66.4 (57.8 to 74.3)
Month 24	52.6 (43.8 to 61.3)	67.9 (59.3 to 75.7)
Month 36	65.4 (56.7 to 73.4)	73.9 (65.6 to 81.1)
Month 42	66.9 (58.2 to 74.8)	73.9 (65.6 to 81.1)

Kaplan-Meier estimates of time to first MMR

	Imatinib	Nilotinib
Number of Participants Analyzed [units: participants]	133	134
Kaplan-Meier estimates of time to first MMR (units: months) Median (95% Confidence Interval)	21.7 (16.5 to 25.2)	8.1 (5.6 to 11.1)

Durable MMR rate at 24 months

	Imatinib	Nilotinib
Number of Participants Analyzed [units: participants]	133	134
Durable MMR rate at 24 months (units: Perentage of Participants) Number (95% Confidence Interval)	27.8 (20.4 to 36.3)	50.7 (42.0 to 59.5)

Kaplan-Meier estimates of duration of first MMR among patients who achieved MMR

	Imatinib	Nilotinib
Number of Participants Analyzed [units: participants]	133	134
Kaplan-Meier estimates of duration of first MMR	NA (NA to NA)[]	NA (NA to NA)[]

among patients who achieved MMR
(units: Months)
Median (95% Confidence Interval)

[1] The median was not reached.

Best complete Cytogenic Response (CCyR) rate by each time point

	Imatinib	Nilotinib
Number of Participants Analyzed [units: participants]	133	134
Best complete Cytogenic Response (CCyR) rate by each time point (units: Percentage of Participants) Number (95% Confidence Interval)		
Overall	89.5 (83.0 to 94.1)	85.8 (78.7 to 91.2)
Month 6	57.1 (48.3 to 65.7)	66.4 (57.8 to 74.3)
Month 12	80.5 (72.7 to 86.8)	77.6 (69.6 to 84.4)
Month 18	84.2 (76.9 to 90.0)	80.6 (72.9 to 86.9)
Month 30	88.0 (81.2 to 93.0)	84.3 (77.0 to 90.0)
Month 24	86.5 (79.5 to 91.8)	83.6 (76.2 to 89.4)
Month 36	89.5 (83.0 to 94.1)	85.8 (78.7 to 91.2)
Month 42	89.5 (83.0 to 94.1)	85.8 (78.7 to 91.2)

Kaplan-Meier estimates of time to first CCYR

	Imatinib	Nilotinib
Number of Participants Analyzed [units: participants]	133	134
Kaplan-Meier estimates of time to first CCYR (units: months) Median (95% Confidence Interval)	6.1 (5.6 to 6.6)	5.6 (5.6 to 6.2)

Kaplan-Meier estimates of duration of first CCyR among patients who achieved CCyR

	Imatinib	Nilotinib
Number of Participants Analyzed [units: participants]	133	134
Kaplan-Meier estimates of duration of first CCyR among patients who achieved CCyR (units: Months) Median (95% Confidence Interval)	NA (NA to NA)[1]	NA (NA to NA)[1]

[1] The median was not reached.

Kaplan-Meier estimates of time to progression to accelerated phase/blast crisis (AP/BC) on treatment

	Imatinib	Nilotinib
Number of Participants Analyzed [units: participants]	133	134
Kaplan-Meier estimates of time to progression to	NA (NA to NA)[1]	NA (NA to NA)[1]

accelerated phase/blast crisis (AP/BC) on treatment
(units: Months)
Median (95% Confidence Interval)

[1] The median was not reached.

Kaplan-Meier estimates of Event-free Survival (EFS) on treatment

	Imatinib	Nilotinib
Number of Participants Analyzed [units: participants]	133	134
Kaplan-Meier estimates of Event-free Survival (EFS) on treatment (units: Months) Median (95% Confidence Interval)	NA (NA to NA)[1]	NA (NA to NA)[1]

[1] The median was not reached.

Kaplan-Meier estimates of progression-free Survival (PFS) on treatment

	Imatinib	Nilotinib
Number of Participants Analyzed [units: participants]	133	134
Kaplan-Meier estimates of progression-free Survival (PFS) on treatment (units: Months) Median (95% Confidence Interval)	NA (NA to NA)[1]	NA (NA to NA)[1]

[1] The median was not reached.

Kaplan-Meier estimates of Overall Survival (OS) on treatment

	Imatinib	Nilotinib
Number of Participants Analyzed [units: participants]	133	134
Kaplan-Meier estimates of Overall Survival (OS) on treatment (units: Months) Median (95% Confidence Interval)	NA (NA to NA)[1]	NA (NA to NA)[1]

[1] Median could not be reached.

Best Complete Hematologic Response (CHR)

	Imatinib	Nilotinib
Number of Participants Analyzed [units: participants]	133	134
Best Complete Hematologic Response (CHR) (units: Percentage of participants) Number (95% Confidence Interval)		
Overall	94.7 (89.5 to 97.9)	94.8 (89.5 to 97.9)
Month 1	66.2 (57.5 to 74.1)	73.1 (64.8 to 80.4)
Month 3	91.0 (84.8 to 95.3)	91.8 (85.8 to 95.8)
Month 4	93.2 (87.5 to 96.9)	93.3 (87.6 to 96.9)
Month 5	94.0	93.3

	(88.5 to 97.4)	(87.6 to 96.9)
Month 6	94.7 (89.5 to 97.9)	93.3 (87.6 to 96.9)
Month 9	94.7 (89.5 to 97.9)	93.3 (87.6 to 96.9)
Month 12	94.7 (89.5 to 97.9)	94.0 (88.6 to 97.4)
Month 15	94.7 (89.5 to 97.9)	94.0 (88.6 to 97.4)
Month 18	94.7 (89.5 to 97.9)	94.8 (89.5 to 97.9)
Month 21	94.7 (89.5 to 97.9)	94.8 (89.5 to 97.9)
Month 24	94.7 (89.5 to 97.9)	94.8 (89.5 to 97.9)
Month 30	94.7 (89.5 to 97.9)	94.8 (89.5 to 97.9)
Month 36	94.7 (89.5 to 97.9)	94.8 (89.5 to 97.9)
Month 39	94.7 (89.5 to 97.9)	94.8 (89.5 to 97.9)
Month 42	94.7 (89.5 to 97.9)	94.8 (89.5 to 97.9)

Modified ELN2009 Criteria

	Imatinib	Nilotinib
Number of Participants Analyzed [units: participants]	133	134
Modified ELN2009 Criteria (units: Percentage of Participants)		

Optimal Response	39.8	55.2
Suboptimal Response	41.4	24.6
Treatment Failure	16.5	14.9
Discontinued	2.3	5.2

Actual Dose Intensity

	Imatinib	Nilotinib
Number of Participants Analyzed [units: participants]	132	133
Actual Dose Intensity (units: mg/day) Mean ± Standard Deviation	416.0 ± 62.40	536.4 ± 99.07

Summary Statistics of trough Imatinib and major metabolite CGP74588 of Imatinib and Nilotinib PK concentration by time point

	Imatinib	CGP74588	Nilotinib
Number of Participants Analyzed [units: participants]	93	93	130
Summary Statistics of trough Imatinib and major metabolite CGP74588 of Imatinib and Nilotinib PK concentration by time point (units: ng/mL) Mean ± Standard Deviation			
Day 8 (Cycle 1)	1235.3 ± 632.36	255.4 ± 154.74	1036.8 ± 618.10
Day 28 (Cycle 1)	1291.3 ± 553.44	288.9 ± 130.25	970.4 ± 606.89

Day 84 (Cycle 3)	1137.8 ± 461.50	235.7 ± 104.31	1172.4 ± 656.25
Day 168 (Cycle 6)	1078.2 ± 413.99	243.2 ± 88.66	1154.8 ± 1034.15
Day 336 (Cycle 12)	1111.1 ± 434.85	238.7 ± 89.11	1370.5 ± 878.88
Average trough PK	1188.7 ± 452.24	258.7 ± 112.88	1137.4 ± 631.31

Summary of Safety

Safety Results

Serious Adverse Events by System Organ Class

	Imatinib 400 mg qd N = 132	Nilotinib 300 mg bid N = 133
Total participants affected	13 (9.85%)	11 (8.27%)
Blood and lymphatic system disorders		
Bone marrow failure[1, †]	1 (0.76%)	3 (2.26%)
Granulocytopenia[1, †]	1 (0.76%)	0 (0.00%)
Thrombocytopenia[1, †]	1 (0.76%)	0 (0.00%)
Thrombocytopenic purpura[1, †]	1 (0.76%)	0 (0.00%)
Thrombocytosis[1, †]	1 (0.76%)	0 (0.00%)

Eye disorders		
Diabetic retinopathy[1, †]	0 (0.00%)	1 (0.75%)
Gastrointestinal disorders		
Abdominal pain[1, †]	0 (0.00%)	1 (0.75%)
Infections and infestations		
Anal abscess[1, †]	1 (0.76%)	0 (0.00%)
Upper respiratory tract infection bacterial[1, †]	0 (0.00%)	1 (0.75%)
Injury, poisoning and procedural complications		
Ankle fracture[1, †]	1 (0.76%)	0 (0.00%)
Lower limb fracture[1, †]	0 (0.00%)	1 (0.75%)
Pelvic fracture[1, †]	0 (0.00%)	1 (0.75%)
Investigations		
Blast cell count increased[1, †]	1 (0.76%)	0 (0.00%)
Neutrophil count decreased[1, †]	0 (0.00%)	1 (0.75%)
Platelet count decreased[1, †]	0 (0.00%)	3 (2.26%)
White blood cell count decreased[1, †]	0 (0.00%)	1 (0.75%)
Metabolism and nutrition disorders		
Diabetes mellitus[1, †]	0 (0.00%)	1 (0.75%)

Musculoskeletal and connective tissue disorders		
Intervertebral disc protrusion[1, †]	1 (0.76%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Cervix carcinoma stage 0[1, †]	1 (0.76%)	0 (0.00%)
Non-Hodgkin's lymphoma recurrent[1, †]	1 (0.76%)	0 (0.00%)
Oesophageal squamous cell carcinoma[1, †]	1 (0.76%)	0 (0.00%)
Nervous system disorders		
Cerebral haemorrhage[1, †]	1 (0.76%)	1 (0.75%)
Renal and urinary disorders		
Urinary retention[1, †]	0 (0.00%)	1 (0.75%)
Reproductive system and breast disorders		
Ovarian rupture[1, †]	1 (0.76%)	0 (0.00%)
Prostatic obstruction[1, †]	0 (0.00%)	1 (0.75%)
Respiratory, thoracic and mediastinal disorders		
Hydrothorax[1, †]	1 (0.76%)	0 (0.00%)

† Systematic Assessment
1 17.1

Other Adverse Events by System Organ Class

Frequent Event Reporting Threshold 5%

	Imatinib 400 mg qd N = 132	Nilotinib 300 mg bid N = 133
Total participants affected	124 (93.94%)	131 (98.50%)
Blood and lymphatic system disorders		
Anaemia[1, †]	18 (13.64%)	12 (9.02%)
Leukopenia[1, †]	35 (26.52%)	27 (20.30%)
Neutropenia[1, †]	18 (13.64%)	7 (5.26%)
Thrombocytopenia[1, †]	37 (28.03%)	41 (30.83%)
Eye disorders		
Eyelid oedema[1, †]	25 (18.94%)	4 (3.01%)
Gastrointestinal disorders		
Abdominal pain upper[1, †]	3 (2.27%)	8 (6.02%)
Diarrhoea[1, †]	18 (13.64%)	5 (3.76%)
Nausea[1, †]	14 (10.61%)	5 (3.76%)
Vomiting[1, †]	14 (10.61%)	3 (2.26%)

General disorders and administration site conditions		
Face oedema[1, †]	11 (8.33%)	0 (0.00%)
Pyrexia[1, †]	15 (11.36%)	12 (9.02%)
Hepatobiliary disorders		
Hyperbilirubinaemia[1, †]	4 (3.03%)	40 (30.08%)
Infections and infestations		
Influenza[1, †]	7 (5.30%)	5 (3.76%)
Nasopharyngitis[1, †]	25 (18.94%)	17 (12.78%)
Upper respiratory tract infection[1, †]	13 (9.85%)	10 (7.52%)
Investigations		
Alanine aminotransferase increased[1, †]	16 (12.12%)	28 (21.05%)
Apolipoprotein B increased[1, †]	3 (2.27%)	9 (6.77%)
Aspartate aminotransferase increased[1, †]	9 (6.82%)	13 (9.77%)
Bilirubin conjugated increased[1, †]	3 (2.27%)	15 (11.28%)
Blood bilirubin increased[1, †]	8 (6.06%)	41 (30.83%)
Blood creatine phosphokinase increased[1, †]	12 (9.09%)	6 (4.51%)
Blood phosphorus	10 (7.58%)	10 (7.52%)

decreased[1, †]		
Gamma-glutamyltransferase increased[1, †]	3 (2.27%)	15 (11.28%)
Haemoglobin decreased[1, †]	14 (10.61%)	8 (6.02%)
Lipase increased[1, †]	29 (21.97%)	37 (27.82%)
Low density lipoprotein increased[1, †]	3 (2.27%)	11 (8.27%)
Neutrophil count decreased[1, †]	16 (12.12%)	15 (11.28%)
Platelet count decreased[1, †]	30 (22.73%)	23 (17.29%)
White blood cell count decreased[1, †]	28 (21.21%)	16 (12.03%)
Metabolism and nutrition disorders		
Hypercholesterolaemia[1, †]	2 (1.52%)	12 (9.02%)
Hyperglycaemia[1, †]	5 (3.79%)	10 (7.52%)
Hypertriglyceridaemia[1, †]	10 (7.58%)	12 (9.02%)
Hypokalaemia[1, †]	13 (9.85%)	4 (3.01%)
Hypophosphataemia[1, †]	17 (12.88%)	15 (11.28%)
Musculoskeletal and connective tissue disorders		
Arthralgia[1, †]	9 (6.82%)	2 (1.50%)
Myalgia[1, †]	8 (6.06%)	16 (12.03%)
Nervous system disorders		
Dizziness[1, †]	8 (6.06%)	2 (1.50%)

Headache[1, †]	4 (3.03%)	12 (9.02%)
Respiratory, thoracic and mediastinal disorders		
Cough[1, †]	9 (6.82%)	4 (3.01%)
Skin and subcutaneous tissue disorders		
Rash[1, †]	17 (12.88%)	47 (35.34%)

† Systematic Assessment
1 17.1

Conclusion:

Month 12 clinical study report

The study met its primary endpoint. The rate of MMR at 12 months was statistically significantly higher in the nilotinib arm compared to the imatinib arm.

The secondary endpoint of best CCyR rate by 12 months was similar between the nilotinib and imatinib arms. However, the best CCyR rate by 6 months was higher in the nilotinib arm, which shows patients in the nilotinib arm achieved CCyR earlier.

The trough concentrations of nilotinib obtained in Chinese patients were found to remain relatively stable over the 12-cycle treatment course, and are comparable with the global trough PK population (CAMN107A2303).

Month 24 clinical study report

The MMR rate and the durable MMR rate at 24 months were both consistently higher for patients in the nilotinib arm compared to the imatinib arm. No difference was observed between the two treatment arms regarding the CCyR rate.

Month 36 clinical study report

The MMR rate at 36 months was higher in the nilotinib arm compared to the imatinib arm. As expected from the previous analyses, no difference was observed between the two treatment arms regarding the CCyR rate.

The proportion of patients with a progression-free survival event on treatment and on study was similar between the two treatment arms at 36 months. The proportion of patients with an event-free survival event (EFS) was slightly higher in the nilotinib arm compared to imatinib and the estimated rates of EFS were similar between the two treatment arms. The estimated rate of patients alive at 36 months was 96.9% in the nilotinib arm and 96.1% in the imatinib arm.

In conclusion: The results of this final analysis confirm that nilotinib is a highly efficacious first-line treatment in Chinese patients with newly diagnosed Ph+ CML-CP. The primary analysis major molecular response (MMR) endpoint was met and showed superiority over imatinib. No new safety findings were identified for either drug in this study. The overall favorable risk/benefit ratio of nilotinib 300 mg bid as front-line therapy in Ph+ CML-CP is further strengthened by these closeout results.

Date of Clinical Trial Report

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