21 April 2017
EMA/313746/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tasigna

International non-proprietary name: nilotinib

Procedure No. EMEA/H/C/000798/II/0084/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 27 June 2016 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

This grouped variation application consists of three Type II variation applications as follows:

- Update of the 150 mg SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1, and Package Leaflet based on the results from study CAMN107I2201 (ENESTfreedom): A Phase II, single-arm study evaluating nilotinib treatment discontinuation (treatment-free remission (TFR)) in newly-diagnosed patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase (Ph+ CML-CP) who achieved a sustained deep molecular response
- Update of the 150 mg and 200 mg Tasigna SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1, and Package Leaflet based on the results from study CAMN107A2408 (ENESTop): A Phase II, single-arm study evaluating nilotinib treatment discontinuation (treatment-free remission (TFR)) in patients with Ph+ CML-CP who achieved a sustained deep molecular response on nilotinib treatment after switching from imatinib treatment.
- Update of the 200 mg Tasigna SmPC sections 4.8 and 5.1, based on the results from study CAMN107A2405 (ENESTcmr): A Phase III open-label, randomised study to evaluate nilotinib or imatinib treatment in patients with Ph+ CML-CP who have not achieved a deep molecular response after previous imatinib therapy.

Additional changes to the Labelling are proposed to comply with the latest QRD template version 10.

An updated RMP, version 16, is also provided in this application.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Tasigna was designated as an orphan medicinal product EU/3/06/375 on 22 May 2016. Tasigna was designated as an orphan medicinal product in the following indication: chronic myeloid leukaemia.
The modified indications, which are the subject of this application, fall within the above mentioned orphan designation.

Information on paediatric requirements

Not applicable.

Article 8 of the paediatric regulation does not apply to this application, since the authorised medicinal product is not protected by a supplementary protection certificate under Regulation (EC) No 469/2009 or by a patent which qualifies for the granting of the supplementary protection.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Harald Enzmann

Timetable	Actual dates
Submission date	27 June 2016
Start of procedure	16 July 2016
CHMP Rapporteur Assessment Report	8 September 2016
CHMP Co-Rapporteur Assessment Report	20 September 2016
PRAC Rapporteur Assessment Report	21 September 2016
PRAC Outcome	29 September 2016
CHMP members comments	7 October 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	11 October 2016
Request for supplementary information (RSI)	13 October 2016
Submission of responses	21 December 2016
CHMP Rapporteur(s) (Joint) response Assessment Report	27 January 2017
CHMP members comments	10 February 2017
Updated CHMP Rapporteur Assessment Report	N/A
2nd RSI	23 February 2017
Submission of responses	21 March 2017
SAG experts meeting to address questions raised by the CHMP	5 April 2017

Timetable	Actual dates
CHMP Rapporteur(s) (Joint) response Assessment Report	11 April 2017
CHMP members comments	18 April 2017
CHMP opinion	21 April 2017
The CHMP adopted a report on similarity of Tasigna with Sprycel (dasatinib), Bosulif (bosutinib) and Iclusig (ponatinib) on 13 October 2016 (Appendix 1)	13 October 2016

2. Scientific discussion

2.1. Introduction

The current indication for Tasigna is as follows:

Tasigna is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase (SmPC, section 4.1).

The scope of this grouped variation application was the update of the Tasigna Summary of Product Characteristics (SmPC) regarding the possibility of treatment discontinuation in patients who have been treated with Tasigna (nilotinib) for at least three years and have achieved a sustained deep molecular response based on the results from two treatment discontinuation studies, CAMN107I2201 (ENESTfreedom) and CAMN107A2408 (ENESTop).

2.2. Non-clinical aspects

2.2.1. Introduction

The MAH provided a revised ERA. The ERA based on studies submitted in the procedure EMEA/H/C/X/28 and as Follow Up Measure (FUM) 039. Furthermore 2 new studies on identification of transformation products occurring in the water-sediment transformation test OECD 308 and the soil degradation test OECD 307 are now included in the ERA.

2.2.2. Ecotoxicity/environmental risk assessment

PEC values were refined based on market prediction data for 2022. Consequently PEC/PNEC risk quotients were updated in Phase II.

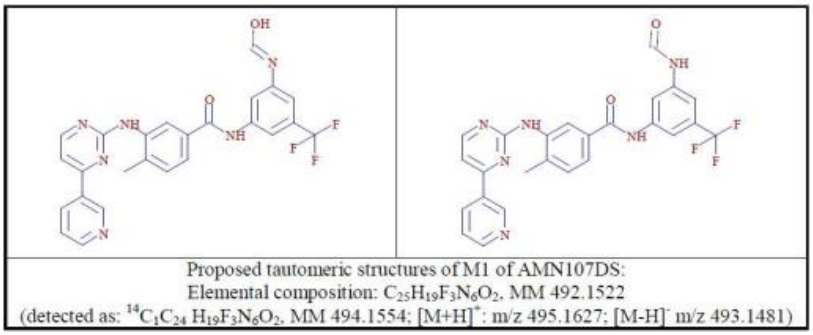
Based on the scientific information available, the placement of the foreseen amounts of nilotinib on the EU market does not constitute any significant risk to surface water, groundwater and terrestrial compartments. However, in the Phase II-Tier B sediment risk assessment a risk is calculated for nilotinib. It should, however, be taken into consideration that no toxicity was found in the study with the sediment-dwelling larvae of Chironomus riparius in a study following OECD testing guideline 219. In this study the upper testing range was limited by the low water solubility of nilotinib and the results of the study are therefore reported as 'no toxicity up to the limit of water solubility'. Based on this fact,

no reliable conclusion on the risk for the sediment compartment is possible.

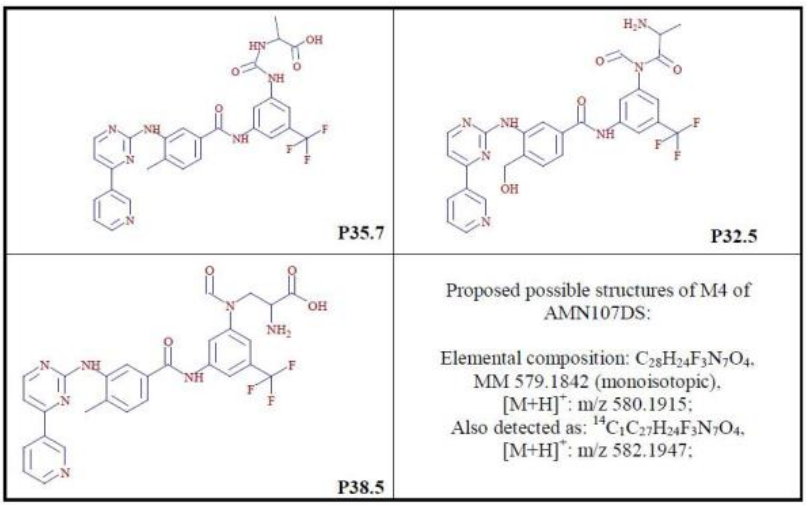
Based on the logarithmic octanol-water partition coefficients of nilotinib of 3.6, a bioconcentration study in fish has been conducted, resulting in a moderate bioconcentration factor of 127. This assessment revealed that nilotinib cannot be considered as a PBT substance based on its low bioconcentration potential in fish. However, nilotinib can be considered as potentially persistent based on the outcome of the studies on transformation in water-sediment systems and soils. Nilotinib showed a half-life of 179-213 days for the total water-sediment systems (normalized to 12°C) and a half-life of 369 days for soils (normalized to 12°C). Consequently the criteria for a very persistent (vP) substance of 180 days in water-sediment systems and soils defined in the REACh guidance on PBT assessment is exceeded for both compartments.

Proposed structure of the transformation products during soil degradation test according to the study protocol OECD 307: Proposed structure of the transformation products during soil degradation test according to the study protocol OECD 307:

M1



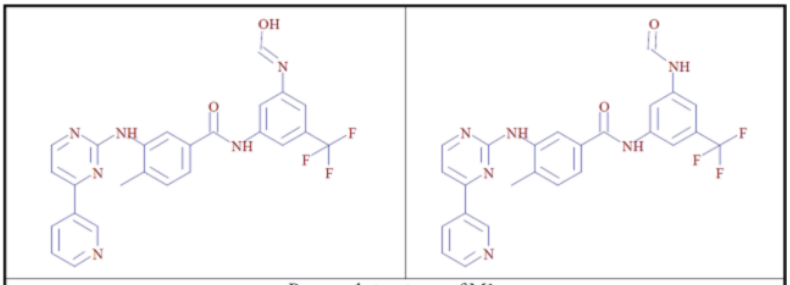
Proposed tautomeric structures of M1 of AMN107DS:
Elemental composition: $C_{25}H_{19}F_3N_6O_2$, MM 492.1522
(detected as: $^{14}C_1C_{24}H_{19}F_3N_6O_2$, MM 494.1554; $[M+H]^+$: m/z 495.1627; $[M-H]^-$ m/z 493.1481)



Proposed possible structures of M4 of AMN107DS:

Elemental composition: $C_{28}H_{24}F_3N_7O_4$,
MM 579.1842 (monoisotopic),
$[M+H]^+$: m/z 580.1915;
Also detected as: $^{14}C_1C_{27}H_{24}F_3N_7O_4$,
$[M+H]^+$: m/z 582.1947;

Proposed structure of the transfomation product in a water-sediment system according to the study protocol OECD 308:



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Elemental composition: $C_{25}H_{19}F_3N_6O_2$, MM 492.1522
(detected as: $^{14}C_1C_{24}H_{19}F_3N_6O_2$, MM 494.1554;
$[M+H]^+$: m/z 495.1627; $[M-H]^-$ m/z 493.1481)

The table of main study results is updated with the new PEC values given in the latest ERA and the normalized DT50 values as described in the paragraph above:

Table 1: Main ERA results

Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (prevalence and proposal for market data, used in Phase II)	4 (default) 0.036 (Prevalence) 0.009	µg/L	> 0.01 threshold Y
Phase II Physical-chemical properties and fate			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$(12°C) = 0.9 - 1.3 d $DT_{50,\ whole\ system}$ (20°C) = 100 d $DT_{50,\ whole\ system}$ (12°C) = 179-213 d 90% shifting to sediment of whole radioactivity on day 7 1 Transformation product > 10% in both test systems (> 30%, stable)	vPt in sediment, identification of transformation product conducted
Phase IIa Effect studies			
Phase IIb Studies			
Aerobic and anaerobic transformation in soil	OECD 307	Worst Case: DT_{50}(20°C) = 172.9 d DT_{50}(12°C) = 369 d % CO_2= 0.3% Bound residues= 26.8% (120 d) 2 Transformation products > 10% (both stable until test end)	vP in soil, Identification of transformation products is completed

2.2.3. Discussion on non-clinical aspects

There is no risk for the aquatic and terrestrial environment. The active ingredient is not considered as PBT substance. However, the active ingredient and its transformation products are very persistent in soil and sediment. The structure of the stable transformation products was proposed in the updated ERA. The conclusion of persistence has been included in the updated ERA.

2.2.4. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of nilotinib.

- Considering the above data, nilotinib should be used according to the precautions stated in section 6.6 of the SmPC in order to minimise any potential risks to the environment: Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2. Overview of key studies

Study	Study details and objectives	No of patients	Dose (mg)	Treatment duration
[Study I2201] or ENESTfreedom	Phase II, single-arm, multi-center nilotinib TFR study in patients with BCR-ABL1 positive CML-CP, who had achieved durable minimal residual disease (MRD) status on first-line nilotinib treatment. Primary objective: to determine the percentage of patients who were in MMR at 48 weeks after starting the TFR phase	215 patients entered the NTCS phase, 190 patients entered the TFR phase	Nilotinib: 300 mg bid or 400 mg qd	52 weeks nilotinib consolidation + 192 weeks observation after nilotinib discontinuation from when the last patient entered the TFR phase
[Study A2408] or ENESTop	Phase II, single-arm, open- label study of TFR in CML-CP patients after achieving sustained MR4.5 on nilotinib. Patients who received at least 3 years of TKI, imatinib as initial TKI treatment (>4 weeks) then switched to nilotinib for at least 2 years prior to study entry. Patients were not to have documented MR4.5 at the time of switch from imatinib to nilotinib. Primary objective: to evaluate the proportion of patients without loss of	163 Ph+ CML-CP patients entered the nilotinib treatment consolidation (NTCS) phase, 126 patients entered the TFR phase	Nilotinib: 300 or 400 mg bid or any other dose received prior to study entry	52 weeks nilotinib consolidation + 192 weeks observation after nilotinib discontinuation from when the last patient entered the TFR phase

Study	Study details and objectives	No of patients	Dose (mg)	Treatment duration
	MMR or confirmed loss of MR4 within 48 weeks following nilotinib cessation.			
[Study A2405] or ENESTcmr	Phase III, open-label, multicenter, randomized study of nilotinib vs. standard imatinib (400/600 mg qd) comparing the kinetics of complete molecular response (CMR) in CML-CP with evidence of persistent leukemia after ≥ 2 years of imatinib therapy. Primary objective: to compare the rate of confirmed best cumulative CMR within the first year of study therapy with nilotinib or imatinib	Total: 207 Nilotinib: 104 Imatinib: 103	Nilotinib: 400 mg bid Imatinib: 400 mg or 600 mg once daily	48 months
Durable MRD- of the 4 last quarterly PCR assessments, the last assessment was MR4.5, no assessment was worse than MR4.0, and no more than two assessments between MR4.0 and MR4.5 CMR- Complete molecular response; defined as undetectable BCR-ABL by RQ-PCR where there is no detectable BCR-ABL/ABL using sensitive molecular monitoring techniques with a sensitivity of MR4.5. MMR = Major Molecular Remission, Loss of MMR is BCR-ABL/ABL > 0.1% based on the International Scale (IS)				

2.4. Clinical efficacy

2.4.1. Dose response studies

- Study I2201 (ENESTfreedom) enrolled patients receiving treatment with nilotinib for newly diagnosed CML-CP. The dose and schedule of nilotinib (300 mg bid) was consistent with the approved first-line indication. Patients who did not tolerate this standard dose but who achieved and/or maintained MR4.5 on a minimum dose of 400 mg once daily continued to be treated at this lower dose of 400 mg once daily at the discretion of the Investigator. Patients who required re initiation of nilotinib treatment because of loss of MMR resumed their previously tolerated nilotinib dose.

- In Study A2408 (ENESTop), Ph+ CML CP patients were allowed to take the same nilotinib dose they were taking prior to study entry. Most patients included in the study were treated with either nilotinib 300 mg or 400 mg bid at study entry. Patients who had achieved and sustained MR4.5 on any dose other than 300 mg/400 mg bid of nilotinib prior to study entry, were also included in the study. The nilotinib 400 mg bid dose is the nilotinib starting dose for second-line treatment.

- In Study A2405 (ENESTcmr) the dose and schedule used (400 mg bid) was consistent with the approved second-line indication.

2.4.2. Main studies

- **STUDY I2201 (ENESTfreedom)**

(ENESTfreedom) was a Phase II, single-arm, multicenter study, evaluating the feasibility of TFR in patients with BCR-ABL1-positive CML-CP who have achieved durable minimal residual disease (MRD) status on first-line nilotinib treatment.

Methods

Study participants

Patients had to have received a minimum of 2 years of first-line nilotinib treatment and have ≥ MR4.5, prior to study entry. During the first 52 weeks of the study (i.e. the NTCS phase), patients were treated with the planned dose of 300 mg bid nilotinib (or at a reduced dose level of 400 mg once daily if required from the perspective of tolerance). Patients had polymerase chain reaction (PCR) assessments every 12 weeks by a Novartis designated laboratory. Patients who achieved durable MRD (i.e. of the 4 last quarterly PCR assessments, the last assessment was MR4.5, no assessment was worse than MR4.0, and no more than two assessments between MR4.0 and MR4.5) were eligible to start the TFR phase, where nilotinib treatment was suspended. During the TFR phase, BCR-ABL/ABL levels were monitored every 4 weeks during the first 48 weeks, every 6 weeks for the following 48 weeks, and every 12 weeks during the last period. All PCR assessments were performed by a Novartis designated laboratory.

During the first 48 weeks of the TFR phase, loss of MR4.0 triggered an intensified bi-weekly BCR-ABL/ABL level monitoring to identify loss of MMR early. Loss of MMR was assessed in a single blood sample (confirmation of loss of MMR was not required) and mandated re-initiation of nilotinib treatment at 300 mg bid or at a reduced dose level of 400 mg once daily if required from the perspective of tolerance within 5 weeks of the collection date of the blood sample demonstrating loss of MMR.

Inclusion criteria

Patients must have met all the inclusion criteria and have met none of the exclusion criteria to enter the study:

1. Male or female patients ≥ 18 years of age.

2. Minimum of two calendar years of nilotinib treatment with at least the last 12 months of nilotinib treatment prior to pre-screening at the approved total daily dose of 600 mg (or at a reduced dose of 400 mg qd if patients did not tolerate the planned dose) for BCR-ABL positive CML in documented chronic phase at the time of diagnosis.

3. Documented chronic phase CML which met all the criteria defined by:

- <15% blasts in peripheral blood and bone marrow
- <30% blasts plus promyelocytes in peripheral blood and bone marrow
- <20% basophils in the peripheral blood
- ≥ 100 x 109/L (≥ 100000/mm3) platelets
- No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly.

4. Patients tolerated a minimum total daily dose of nilotinib of 400 mg.

5. Evidence of typical BCR-ABL transcripts [b3a2 (e14a2) and/or b2a2 (e13a2)] at the time of CML-CP diagnosis i.e. prior to first start of TKI treatment which were amenable to standardized reverse transcriptase PCR quantification.

6. Patient in MR4.5 at pre-screening at a Novartis designated laboratory.

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

8. Adequate end organ function as defined by:

- Direct bilirubin ≤ 1.5 x upper limit of normal (ULN), except for i) patients with documented Gilbert's syndrome for whom any bilirubin value was allowed and ii) for patients with asymptomatic hyperbilirubinemia (liver transaminases and alkaline phosphatase within normal range).
- serum glutamic oxaloacetic transaminase/aspartate aminotransferase and serum glutamic pyruvic transaminase/ alanine aminotransferase ≤ 3 x ULN i.e. equivalent to ≤ grade 1 National Cancer Institue-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4.03.
- Serum lipase ≤ 2 x ULN i.e. equivalent to ≤ grade 2 NCI-CTCAE v.4.03.
- Alkaline phosphatase ≤ 2.5 x ULN.
- Serum creatinine <1.5 x ULN.

9. Patients met the following electrolyte values within normal limits or corrected the values to be within normal limits with supplements prior to first dose of study medication:

- Potassium (suggested in order to prevent issues with QT and/or rhythm abnormalities)
- Magnesium (suggested in order to prevent issues with QT and/or rhythm abnormalities)
- Total calcium (corrected for serum albumin)

10. Patients had normal marrow function as defined:

- Absolute Neutrophil Count ≥ 1.5 x 109/L
- Hemoglobin ≥ 9.0 g/dL
- Platelets ≥ 100 x 109/L

11. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures.

Exclusion criteria

Patients eligible for this study did not meet any of the following criteria:

1. Previous treatment with BCR-ABL inhibitors other than nilotinib for more than a total cumulative duration of four weeks.

2. Previous treatment with alpha-interferon of any duration.

3. Previous anticancer agents for CML other than nilotinib except for cytoreduction after CML diagnosis until up to four weeks after first dose of nilotinib.

4. Known second chronic phase of CML after previous progression to AP/blast crisis (BC).

5. Poorly controlled diabetes mellitus (defined as hemoglobin A1c >9%).

6. Impaired cardiac function including any one of the following:

- Left ventricular ejection fraction <45% or below the institutional lower limit of the normal range (whichever was higher).
- Inability to determine the QT interval on electrocardiogram (ECG), except for patients with evidence of measurable QT interval at the time of CML diagnosis (e.g. prior to first start of TKI treatment) and who had no documented clinical signs of cardiovascular disease and / or clinical signs of conduction abnormality.
- Complete left bundle branch block.
- Right bundle branch block plus left anterior or posterior hemiblock.
- Use of a ventricular-paced pacemaker.
- Congenital 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.
- QTc (Corrected QT Interval) >450 ms on the average of three serial baseline ECG [using the QT interval, Fridericia correction (QTcF) formula]. If QTcF >450 ms and electrolytes were not within normal ranges, electrolytes were corrected and then the patient re-tested for QTc. This exclusion criterion was not applicable for patients with non-measurable QT interval who had evidence of measurable QT interval at the time of CML diagnosis (e.g. prior to first start of TKI treatment) and who had no documented clinical signs of cardiovascular disease and / or clinical signs of conduction abnormality.
- History or clinical signs of myocardial infarction within one year of study entry.
- History of unstable angina within one year of study entry.
- Other clinically significant heart disease (e.g. congestive heart failure, cardiomyopathy or uncontrolled hypertension).

7. Severe and/or uncontrolled concurrent medical disease that in the opinion of the Investigator could cause unacceptable safety risks or compromise compliance with the protocol (e.g. uncontrolled diabetes, uncontrolled infection).

8. History of acute pancreatitis within one year of study entry or past medical history of chronic pancreatitis.

9. Known presence of significant congenital or acquired bleeding disorder unrelated to cancer.

10. History of another active malignancy within five years prior to study entry with the exception of previous or concomitant basal cell skin cancer and previous carcinoma in situ treated curatively.

11. Patients who had not recovered from prior surgery.

12. Treatment with other investigational agents (defined as not used in accordance with the approved indication) within four weeks of Day 1.

13. Patients actively receiving therapy with strong cytochrome P4503A4 (CYP3A4) inhibitors and/or inducers, and the treatment could not be either discontinued or switched to a different medication prior to starting study drug.

14. Patients actively receiving therapy with herbal medicines that are strong CYP3A4 inhibitors and/or inducers, and the treatment could not be either discontinued or switched to a different medication prior

to starting study drug. These herbal medicines included Echinacea, (including E. purpurea, E. angustifolia and E. pallida), Piperine, Artemisinin, St. John's Wort, and Ginkgo.

15. Patients who were currently receiving treatment with any medications that had the potential to prolong the QT interval and the treatment could not be either safely discontinued or switched to a different medication prior to starting study drug.

16. Impairment of gastrointestinal (GI) function or GI disease that might significantly alter the absorption of study drug (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or gastric bypass surgery).

17. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin laboratory test.

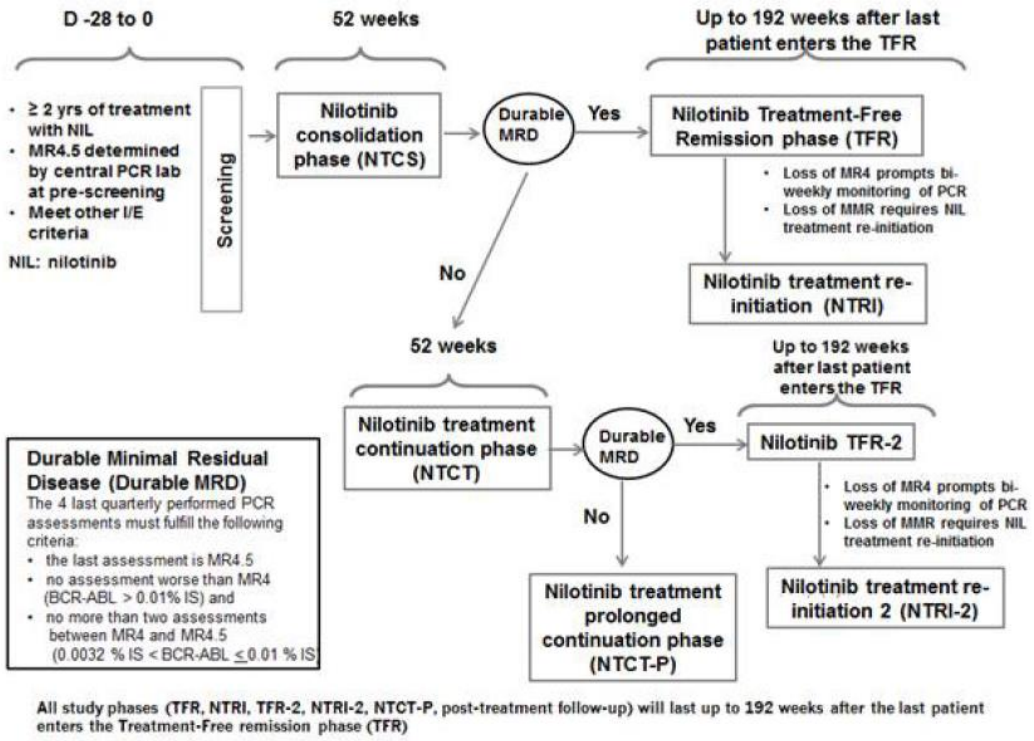
18. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they were using highly effective methods of contraception during the study and for 14 days after the final dose of nilotinib.

Treatments

The study comprised three main phases: the nilotinib consolidation (NTCS) phase (52 weeks), the nilotinib TFR phase (up to 192 weeks after the last patient enters the nilotinib TFR phase) and the treatment re-initiation (NTRI) phase (up to 192 weeks after the last patient entered in the TFR phase).

All eligible patients in the treatment phases (NTCS phase, NTRI and NTRI-2 phases and the NTCT and NTCT-P phases) were treated orally with the planned dose of 300 mg nilotinib bid. Dose regimen could be decreased to 400 mg once daily at the discretion of the Investigator in case of study-drug related hematological and non-hematological toxicities.

Figure 1 Design of Study I2201 (ENESTfreedom)



Objectives

Outcomes/endpoints

The primary efficacy variable in Study I2201 is the proportion of patients who are in MMR (MR3.0) at 48 weeks after starting the TFR phase defined as the number of patients with MMR at 48 weeks after starting the TFR phase with no loss of MMR and no re-initiation of nilotinib therapy in the first 48 weeks after starting the TFR phase divided by the number of patients who entered the TFR phase.

The main secondary efficacy endpoints assessed in the current analysis are:

- Treatment-free survival (TFS) after the start of the TFR phase
- MR4.5 rate at 48 weeks after start of the TFR phase.
- Time required to regain MMR/MR4.5
- Progression free survival (PFS) after the start of the TFR phase
- Overall survival (OS) after the start of the TFR
- Kinetics of BCR-ABL/ABL transcript levels after restart of nilotinib treatment

The exploratory efficacy endpoints assessed in the current analysis are:

- Association between baseline demographics/disease history and primary endpoint

- Patient-reported outcomes and resource utilization (RU)
- BCR-ABL mutations in patients who lost MMR during the TFR phase

Sample size

Demonstration of successful nilotinib TFR phase was based on a study designed with a 90% power to test the null hypothesis that the rate of MMR at 48 weeks after start of the TFR phase was < 50% with the alternative hypothesis that the rate of MMR at 48 weeks after start of the TFR phase was >50%. The sample size was based on Fleming's single stage design to test the null hypothesis H0: $p \leq 0.5$, where p was the rate of MMR at 48 weeks after start of the TFR phase (considering any patient who required re-initiation of treatment as non-responder). If the true rate $p \geq 0.65$, then with one-sided alpha level of 2.5% and a power of 90%, a minimum of 122 patients were required to be studied. This study had actually enrolled 216 patients by 20-Dec-2013, the date when the patient enrollment was closed. With 216 patients enrolled, assuming approximately 30% of enrolled patients who had MR4.5 at study entry would not be eligible for starting the TFR phase, there would have been approximately 151 patients entering TFR. Assuming the true rate of MMR at 48 weeks after start of the TFR phase would be 65%, with a MMR rate of 50% for the null hypothesis, the study would have a 94% power with one-sided alpha level of 2.5% to test the null hypothesis. The power would have increased by 4% based on the 216 enrolled patients compared to the originally planned 90% power based on the 175 enrolled patients, with all the other assumptions for the power calculation being the same.

Randomisation

Blinding (masking)

This was an open-label study.

Statistical methods

The primary efficacy analysis was performed on the FAS. The primary endpoint (rate of successful TFR) was presented together with an exact 95% Clopper-Pearson confidence interval (CI). The null hypothesis was to be rejected if the lower limit of the 95% CI was greater than 0.50. The primary analysis was repeated on the PPS as a supportive analysis. All demographic data, medical history and current medical conditions at study start, and disease history were summarized and listed for the FAS and Safety set.

The rate of molecular responses by certain time points after starting the TFR phase as well as the rate of patients who re-achieved molecular responses (MR4.5/MMR) with nilotinib retreatment were presented together with an exact 95% Clopper-Pearson CI. Kinetics of BCR-ABL transcript levels after re-start of nilotinib therapy were presented by a box-plot of BCR-ABL ratio over time and were also summarized over time.

All time to event endpoints including duration of treatment re-initiation required to regain MMR and MR4.5, TFS, PFS and OS were analyzed using the Kaplan-Meier (KM) method and were presented by KM plots.

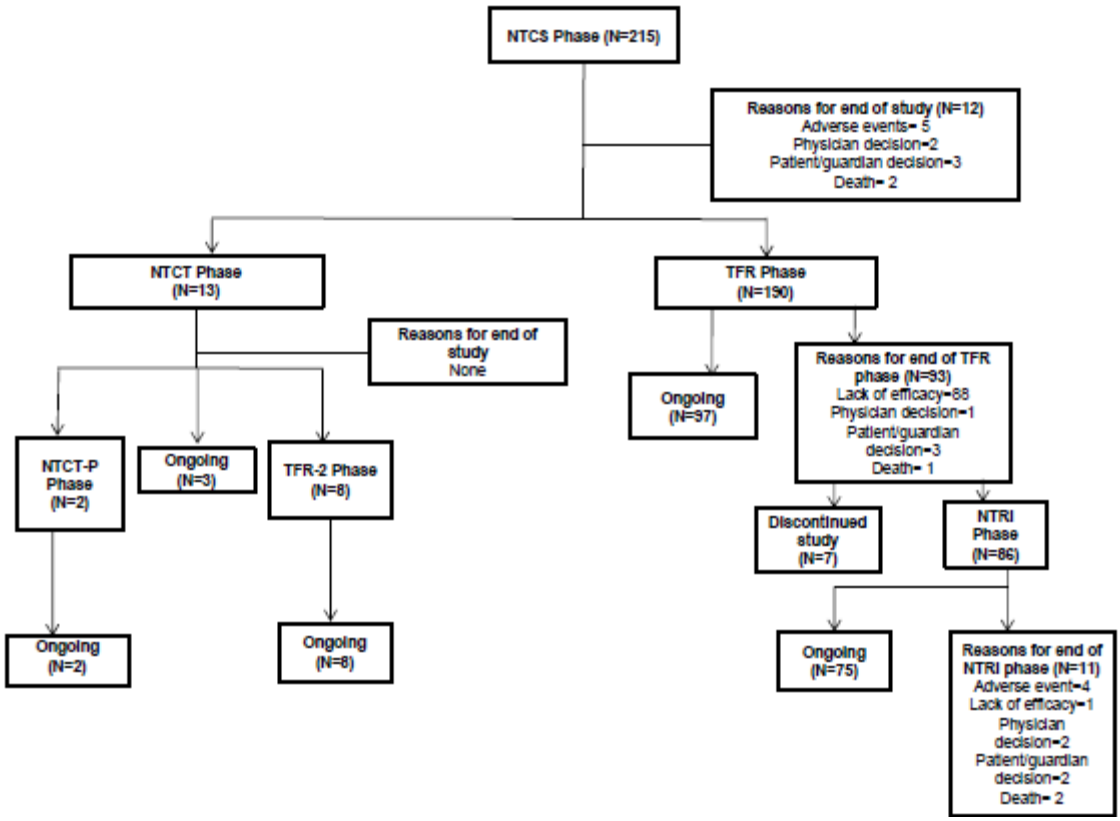
All nilotinib concentrations were listed using the Safety set. The following is the list of analyses conducted to investigate the nilotinib concentration- efficacy relationship: Scatter plot of BCR ABL ratio (%) at 48 weeks of the NTCS phase vs. trough nilotinib concentration and the TFR phase entry status was summarized using contingency table by trough nilotinib concentration categories (by quartiles). Safety set was used for all safety analyses. Since the primary interest of the study was to assess the

benefit of stopping treatment, particular analysis was performed on the patients who entered the TFR phase (TFR Safety set): those analyses focused on the differences of the incidence of safety events (AEs and lab abnormalities) between the NTCS phase and the first 48-weeks of the TFR phase to allow fair comparison.

Results

Participant flow

Figure 2 Patient flow across for the study I2201 (ENESTfreedom)



Recruitment

Study centers: Argentina (2), Austria (5), Belgium (10), Bulgaria (1), Colombia (2), Denmark (1), France (12), Germany (25), Greece (3), Hungary (2), Ireland (2), Italy (15), Japan (12), Netherlands (1), Poland (4), Spain (15), Sweden (3), UK (4), US (13).

Conduct of the study

Protocol amendments

The study protocol was amended three times.

The key features of each amendment are given below.

Amendment 1 (released on 3-Jul-2013): At the time of the amendment the study was in the startup phase; 16 patients had been enrolled as of 20-Jun-2013.

The primary purpose for the amendment was:

- To implement modifications as requested from different Health Authorities (HAs) and Ethic Committees/Institutional Review Boards (ECs/IRBs) during review of the original protocol.
- To address feedback from Investigators received during the study startup.

The main points addressed were:

- Allowed repeated pre-screenings for BCR-ABL transcript level as soon as possible when MR4.5 could not be assessed at pre-screening due to logistical or quality issues which was considered to increase the chance of enrolling patients who were actually eligible for screening/enrollment.
- According to the Novartis "Guideline on Prevention of Pregnancies in Clinical Trials" for highly effective contraception, monthly urine pregnancy testing was included in the assessments schedule. The requirement of using highly effective contraception was changed from 30 to 14 days after the final dose of nilotinib based on the half-life of Tasigna® and the individual variability of metabolism. Additionally the acceptable method of highly effective contraception was corrected for periodic abstinence.
- The criteria for premature withdrawal and how to proceed if a pregnancy occurred during TFR was clarified.
- Inclusion and exclusion criteria were amended to better reflect the patient population to be included in Study I2201 including that patients must have been treated for a minimum of two calendar years with at least the last 12 months prior to pre-screening at the approved total daily dose of 600 mg nilotinib (or at a reduced dose level of 400 mg qd if patients did not tolerate the planned dose).
- Allowed screening patients from Study EIC01 (ENEST1st) study for participation to Study I2201 without having first to discontinue Study EIC01. Patients would discontinue Study EIC01 only if they are confirmed eligible for Study I2201. This practice was in compliance with the ICH Topic E8 guidelines as it constituted a "justified exception".
- Dose reduction guidelines for study-drug related non-hematologic toxicity and suggested management of selected AEs were updated to reflect the latest version of the nilotinib [Investigator Brochure] on Management of Ischemic vascular or Cardiovascular Events.
- Pharmacogenetics study was added to identify factors (i.e. pt. demography, genetic polymorphisms as well as genomic biomarkers) associated with successful TFR of nilotinib therapy. Polymorphisms known to be associated with sub-optimal response to treatment with imatinib, nilotinib or other TKI as well as polymorphisms proposed in the literature as criteria for discontinuing treatment was tested for their association with successful TFR. These might include polymorphisms in NKp30, members of the KIR family and members of the BCL2 family (such as BIM).
- To correct discrepancies and add clarifications within the protocol.

Amendment 2 (released on 03-Jul-2014)

The main purposes of the amendment were:

- To include cholesterol testing in the assessment schedule. Elevations in total serum cholesterol and low density lipoprotein cholesterol was observed very commonly (more than 10%) in patients treated with nilotinib and commonly (between 1 to 10%) in patients treated with imatinib. Most of the cholesterol elevations were grade 1 (>ULN – 300 mg/dL; >ULN - 7.75 mmol/L) or 2 (>300 - 400 mg/dL; >7.75 - 10.34 mmol/L), and some elevations were present prior to initiation of CML therapy. Lipid profiles including total cholesterol, LDL-C and HDL-C were assessed during the

conduct of this study. If test results warranted intervention, Investigators followed their local standards of practice or treatment guidelines which recommended treatment even for grade 1 cholesterol elevation.

Before prescribing a lipid-lowering medication, the possibility of drug-drug interactions was considered due to moderate inhibitory effect of nilotinib on CYP3A4 isoenzyme that was involved in the metabolic pathway of some statins (HMG-CoA reductase inhibitors).

- To provide a harmonization on dose reductions guidelines across Novartis-sponsored Tasigna® study protocols. Hence the dose reduction guidelines for the following non-hematologic toxicities were updated:
    - Pancreatitis grade 4: change from "Hold therapy" to "Stop therapy".
    - QTcF prolongation >480 ms toxicity.
    - Cardiac "Other": change from "Hold therapy" to "Stop therapy".
- To incorporate guidance for the management of:
    - Serum cholesterol increased.
    - Blood glucose increased.
    - Other cardiac risk factors.
    - Ischemic vascular or ischemic cardiovascular events occurring in patients treated with nilotinib.
- To incorporate precaution of use for antacid drugs to be aligned with Tasigna® FDA Prescribing Information and EMA SmPC.
- To define ischemic vascular and ischemic cardiovascular events as AEs of special interest, and their reporting.
- To include serum phosphate testing in the assessment schedule to ensure consistency with the dose reduction guidelines in case of serum hypophosphatemia.
- To clarify the specification of the statistical alternative hypothesis H1.
- To inform the IRBs/IECs/REBs and HAs about over-recruitment and its impact on the stopping rules applied to the first 48 weeks after start of TFR and on the sample size calculation.
- To correct discrepancies and add clarifications within the protocol.

Amendment 3 (released on 30-Jul-2015): At the time of the database lock, the protocol amendment 3 was yet to receive health authority (HA)/Ethics committee (EC)/Independent review board (IRB) approval in five countries.

The main purposes of the amendment were:

- To clarify instructions on when intensified PCR bi-weekly monitoring will be ended if loss of MR4.0 happened after the first 48 weeks of the TFR phase.
- To more precisely define "immediate" treatment re-initiation after loss of MMR.
- To further clarify the early study termination rules during the first 48 weeks of the TFR phase.
- To add a section "General non-hematological laboratory toxicity" to allow for a distinction from "General non-hematology toxicity", for which the described rules must be strictly applied without any possibility of modification by the Investigator. It was necessary to introduce the section

"General non-hematological laboratory toxicity" to accommodate an individual assessment by the Investigator in some clinical situations such as serum glucose increase ≥ grade 2 or bilirubin increase ≥ grade 2 in Gilbert's patients lasting longer than 28 days even upon dose reduction of study drug, which were not harmful to the patient or was typical, and could be transient during the management of concomitant disease (e.g. diabetes mellitus). In such situations, stopping of study medication might not be appropriate and this new section could avoid that such patients had to be withdrawn from study for medically unjustifiable reasons.

- To clarify that strong CYP3A4 inhibitors and QT interval prolonging agents are considered as prohibited concomitant medications during the whole duration of the study.
- To include retrospective collection of Sokal risk category at diagnosis parameters.
- To introduce additional guidance for Investigators to differentiate between patients who discontinued certain clinical trial protocol elements (e.g., discontinued study treatment, or some or all visits etc.), who withdrew consent or who were lost to follow-up.

Other changes in study conduct

There were no changes that occurred in the study conduct.

Changes in planned analysis

The original report and analysis plan (RAP Module 3) was finalized and approved on 02-Apr-2014, which was aligned with protocol Section 10 (including protocol amendment 1).

The RAP Module 3 was amended (Amendment 1) on 22-Sep-2015 before the database lock for the primary analysis, with the following main changes in the planned analysis.

- Added analysis descriptions for the exploratory analyses to identify potential predictive factors for successful TFR.
- Updated reporting of deaths to also describe causes of deaths (and not only number of deaths) post study discontinuation in the Survival follow-up period.
- Provided descriptions on summarizing the data for PROs and healthcare resource utilization.

The RAP Module 3 was amended (Amendment 2) on 01-Feb-2016 before the database lock for the primary analysis, with the following main changes in the planned analysis:

- Clarified that in analyses comparing consolidation to TFR, only the first year of TFR will be taken into account to allow fair comparison between the 2 periods;
- Removed the EQ-5D-5L health index score from planned CSR analyses as it would not be relevant to compute it for the entire study population, but rather only if needed for a specific country/region population and adapted to this particular country/region;
- Modified the criteria of evaluable PK trough samples for the Pharmacokinetic Analysis Set (PAS) according to PK dosing and sampling date/time;
- Acknowledged the fact that the Sokal risk score data may not be available for a significant proportion of patients at the time of primary analysis and that it may not allow evaluating the impact of Sokal risk group on the primary endpoint.

On 24-Mar-2016, after the database lock, the RAP Module 3 was amended (Addendum 1) with the following main changes in the planned analyses:

- Correct the formulas for calculating the severity score and interference score for MDASI-CML.

- Added exploratory analyses to further characterize the recurrence, time to appearance and duration of AEs in the grouping musculoskeletal pain.

Baseline data

The baseline data including the demographic characteristics of patients, the disease history and Prior antineoplastic treatment with nilotinib are summarised in the below tables:

Table 3 Demographic characteristics - Study I2201 (FAS)

Demographic variable	All patients N=190
Age (years)	
n	190
Mean (SD)	53.6 (13.46)
Median	55.0
25th - 75th percentiles	44.0-63.0
Min-Max	21-86
Age category -n (%)	
< 35 years	16 (8.4)
≥ 35 - < 45 years	33 (17.4)
≥ 45 - < 55 years	45 (23.7)
≥ 55 - < 65 years	56 (29.5)
≥ 65 years	40 (21.1)
Sex -n (%)	
Male	96 (50.5)
Female	94 (49.5)
Race -n (%)	
Caucasian	167 (87.9)
Asian	18 (9.5)
Unknown	3 (1.6)
Native American	1 (0.5)
Other	1 (0.5)
Ethnicity -n (%)	
Other	102 (53.7)
Not Reported	26 (13.7)
Hispanic Or Latino	23 (12.1)
Unknown	19 (10.0)
East Asian	16 (8.4)
West Asian	3 (1.6)
Russian	1 (0.5)
ECOG performance status -n (%)	
0	175 (92.1)
1	14 (7.4)
2	1 (0.5)

Table 4 Disease history Study I2201 (FAS)

Characteristic	All patients N=190
Time since initial diagnosis of CML until study entry (months)	
n	190
Mean (SD)	33.55 (8.403)
Median	32.18
Min-Max	21.4-80.7
Time since first MR4.5 until study entry (months)	
n	190
Mean (SD)	16.30 (13.129)
Median	18.28
Min-Max	0.3-70.9
Sokal risk score at diagnosis -n (%)	
Low	25 (13.2)
Intermediate	25 (13.2)
High	12 (6.3)
Missing	128 (67.4)

Table 5 Prior antineoplastic treatment with nilotinib – Study I2201 (FAS)

Characteristic	All patients N=190
Duration on nilotinib treatment prior to TFR phase entry (months)	
n	190
Mean (SD)	44.54 (8.152)
Median	43.47
Min - Max	32.9-88.7
Daily dose of Nilotinib prior to TFR phase entry (mg), n (%)	
400	11(5.8)
450	1 (0.5)
600	178 (93.7)*

*There were 11 patients who had been on 300 mg bid (600 mg/day) before the last day prior to TFR phase entry. On the last day prior to TFR phase, these patients only took 300 mg once daily (300 mg/day).

Numbers analysed

Table 6 Analysis sets, by study phase (Safety set)

Analysis set	NTCS phase N=215 n (%)	TFR phase N=190 n (%)	NTRI phase N=86 n (%)	NTCT phase N=13 n (%)	TFR-2 phase N=8 n (%)	NTRI-2 phase N=0 n (%)	NTCT-P phase N=2 n (%)
Full analysis set	NA	190 (100)	NA	NA	NA	NA	NA
Safety set (1)	215 (100)	190 (100)	86 (100)	13 (100)	8 (100)	0	2 (100)
Per-Protocol set	NA	184 (96.8)	NA	NA	NA	NA	NA
Pharmacokinetic analysis set	115 (53.5)	NA	NA	NA	NA	NA	NA

NTCS=nilotinib treatment consolidation; TFR=treatment-free remission;
NTCT=nilotinib treatment continuation; NTRI=nilotinib treatment re-initiation;
NTCT-P=nilotinib treatment prolonged continuation.
N is the number of patients who entered the study phase.
(1) Patients are summarized according to study phases.

Outcomes and estimation

Primary endpoint: MMR rate at 48 weeks

Table 7 Propotion of patients in MMR at 48 weeks after starting the TFR phase with retreated patients as non-responders Study I2201 (FAS)

	TFR phase N=190	
	n (%)	95% CI
Response		
MMR	98 (51.6)	(44.2, 58.9)

- N: The total number of patients in the TFR phase. It is the denominator for percentage (%) calculation.
- n: Number of patients who are at the corresponding category.
- The 95% CI for the frequency distribution was computed using exact Clopper-Pearson method.

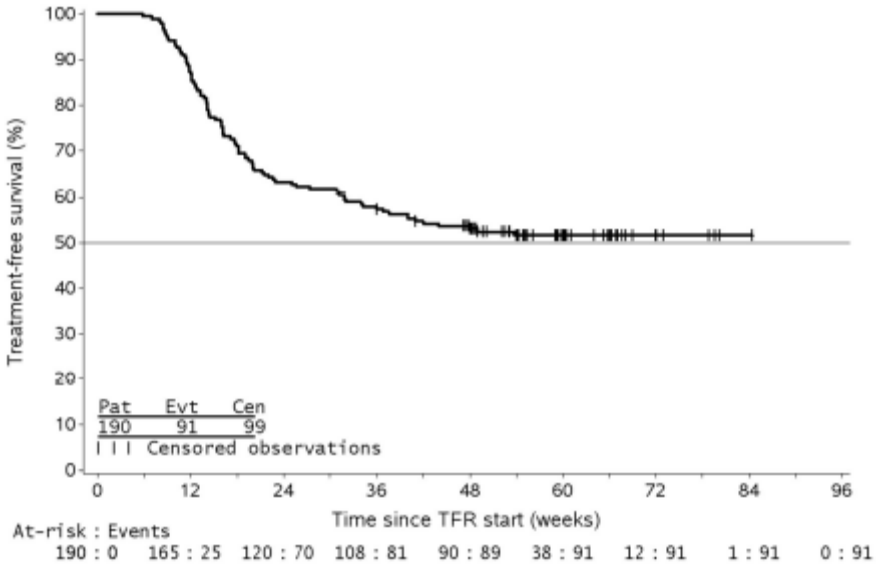
Secondary endpoint: TFS after the start of the TFR phase

Table 8 TFS after start of the TFR phase - Study I2201 (FAS)

Category	TFR phase N = 190
Number of events – n (%)	91 (47.9)
Number censored – n (%)	99 (52.1)
Percentiles (weeks) (95% CI)	
25th percentile	16.1 (14.0,19.0)
Median	NE (36.9,NE)
75th percentile	NE
Kaplan-Meier estimate (%) (95% CI)	
4 weeks	100.0 (100.0, 100.0)
8 weeks	98.4 (95.2, 99.5)
12 weeks	86.8 (81.2, 90.9)
16 weeks	75.3 (68.5, 80.8)
20 weeks	66.3 (59.1, 72.5)
24 weeks	63.2 (55.9, 69.6)
36 weeks	57.4 (50.0, 64.0)
48 weeks	53.1 (45.7, 59.9)

NE: Not estimable

Figure 3 Kaplan-Meier estimates of TFS after start of the TFR phase - Study I2201 (FAS)



Secondary endpoint: MR4.5 rate at 48 weeks after start of the TFR phase

Table 9 MR4.5 rate at 48 weeks after starting the TFR phase – Study I2201 (FAS)

	TFR phase N=190	
	n (%)	95% CI
Response		
MR4.5	90 (47.4)	(40.1,54.7)

The 95% CI for the frequency distribution was computed using exact Clopper-Pearson method.

Secondary endpoint: Time required to regain MMR/MR4.5

Table 10 Kaplan-Meier estimate of time required to regain MMR –Study I2201 (NTRI Safety set)

Category	NTRI N = 86
Number of events – n (%)	85 (98.8)
Number censored – n (%)	1 (1.2)
Percentiles (95% CI) (weeks)	
25th percentile	4.3 (4.1,4.9)
Median	7.9 (5.1,8.0)
75th percentile	8.1 (8.1,9.1)
Kaplan-Meier estimate (95% CI)	
4 weeks	8.1 (4.0, 16.3)
8 weeks	61.9 (51.8, 72.1)
12 weeks	92.9 (86.1, 97.1)
16 weeks	96.4 (90.8, 99.0)
20 weeks	97.6 (92.5, 99.5)
24 weeks	98.8 (94.2, 99.9)

Table 11 Kaplan-Meier estimate of time required to regain MMR in the NTRI phase – Study I2201 (NTRI Safety set)

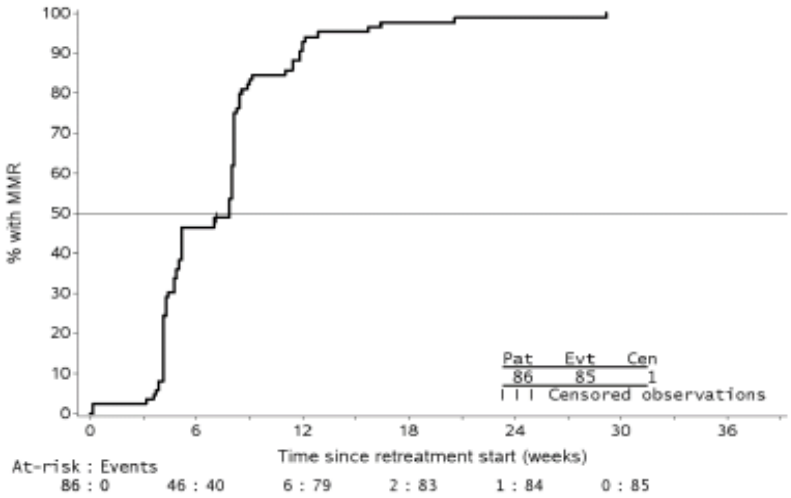
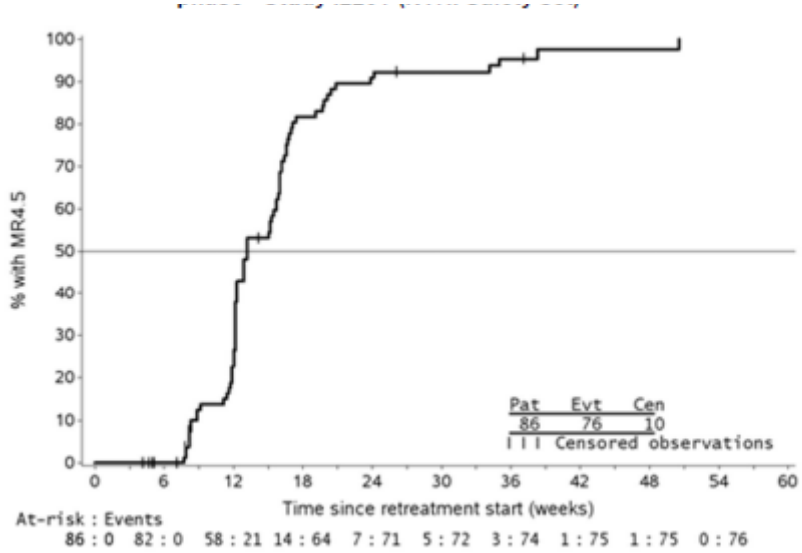


Table 12 Time required to regain MR4.5 – Study I2201 (NTRI Safety set)

Category	NTRI N = 86
Number of events – n (%)	76 (88.4)
Number censored – n (%)	10 (11.6)
Percentiles (95% CI)	
25th percentile	12.0 (11.1,12.1)
Median	13.1 (12.3,15.7)
75th percentile	16.6 (16.0,19.7)
Kaplan-Meier estimate (95% CI)	
4 weeks	0.0 (0.0, 0.0)
8 weeks	3.7 (1.2, 11.0)
12 weeks	26.5 (18.1, 37.7)
16 weeks	68.7 (58.3, 78.6)
20 weeks	85.7 (76.9, 92.4)
24 weeks	90.9 (83.2, 96.0)
36 weeks	95.3 (88.6, 98.7)
48 weeks	97.7 (90.6, 99.7)

Table 13 Kaplan-Meier estimate of time required to regain MR 4.5 in the NTRI phase –Study I2201 (NTRI Safety set)



Secondary endpoint: PFS after the start of the TFR phase

As of the data cut-off date, three PFS events (all deaths not considered CML-related) were observed after the start of the TFR phase, and 187 (98.4%) patients were censored for PFS analysis. The estimated PFS rate at 48 weeks after the start of the TFR phase was 98.9% (95% CI: 95.7, 99.7)

Secondary endpoint: OS after the start of the TFR phase

As of the data cut-off date, three patients died after the start of the TFR phase (one in the TFR phase and two in the re-initiation phase) and 187 patients were alive and censored for OS analysis. The estimated OS rate at 48 weeks after the start of the TFR phase was 98.9% (95% CI: 95.8, 99.7)

Ancillary analyses

Analysis of identifying predictors for successful TFR

Successful TFR is defined according to the primary endpoint definition (patients in MMR at 48 weeks of TFR). Various analyses were done to evaluate the impact of potential predictive factors on the primary endpoint (in the FAS population, all patients who entered the TFR phase). In the patients who entered the TFR phase (FAS), between study entry and entry in the TFR phase, there is by protocol a fixed duration of 52 weeks during which all patients in FAS had to remain on nilotinib treatment and minimum residual disease before entering in the TFR phase. This means that the effect of 1) the duration of prior nilotinib treatment up to study entry, and 2) of the time from the first MR4.5 up to the time of study entry on whether successful TFR occurred is equivalent to the effect of the time up to TFR entry. Therefore, the conclusions regarding the impact of these factors as analyzed up to study entry can be transposed to that of the same factors up to the TFR entry.

- Multivariate logistic regression analysis for successful TFR with age, gender, duration of prior nilotinib treatment and time since first MR4.5 until study entry as explanatory variables, did not provide evidence of strong predictors of successful TFR. The Stepwise selection model (with level of 0.1 for both variable entry and stay) selected only one variable, time since MR4.5 until study entry, as a potential predictor of successful TFR (odds ratio 1.027 [95% CI: 1.003, 1.051], [Study I2201-Table 14.2-5.5]).
- The duration of prior nilotinib treatment before study entry was not shown to be a strong predictor of successful TFR in this study, probably due to the fact that the durations of prior nilotinib treatment did not differ substantially among all patients in FAS (mean [SD]: 32.6 [8.14] months.
- Baseline demographics and prior disease characteristics were also summarized for patients who achieved successful TFR vs. patients who did not achieve successful TFR but it did not show a notable difference between patients achieving successful TFR and patients without successful TFR.

In summary, no strong predictor of successful TFR was identified. There was no notable difference in baseline demographics, disease characteristics and prior treatment or prior response characteristics between patients who had successful TFR and patients who did not have successful TFR.

BCR-ABL mutations in patients who lost MMR during the TFR phase

A thorough inventory of clinical BCR-ABL compound mutations associated with TKI resistance reported in the published literature identified a limited list of 12 kinase domain positions comprising the majority of compound mutations, which are referred to as key positions. The key residues in the native BCR-ABL kinase domain are: M244, G250, Q252, Y253, E255, V299, F311, T315, F317, M351, F359, and H396 (Zabriskie et al 2014). Eighty-nine patients (46.8%) lost MMR during the TFR phase. Amongst these 89 patients, 72 patients had at least one evaluable mutational analysis performed. Amongst the 72 patients evaluable for mutational analysis, the BCR-ABL mutation of F359V (mutation of less sensitivity to nilotinib) was detected in one patient (0.5%).

- **STUDY A2408 (ENESTop)**

(ENESTop) was a Phase II, single-arm, multi-center study, evaluating the feasibility of TFR post TKI treatment in patients with BCR-ABL1-positive CML-CP. This study was designed to determine the rate of successful TFR in patients who achieved and maintained MR4.5 on nilotinib.

Methods

Study participants

Inclusion criteria

1. Male or female patients ≥ 18 years of age.

2. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2.

3. Patient diagnosed with BCR-ABL positive CML-CP

4. Patient has received a minimum of three years of TKI treatment (first with imatinib for > four weeks and then switched to nilotinib) since initial diagnosis.

5. Patient received at least two years of nilotinib treatment prior to study entry.

6. Patient achieved MR4.5 during nilotinib treatment as determined by a Novartis designated laboratory at screening.

7. Adequate end organ function as defined by:

- Direct bilirubin ≤ 1.5 x upper limit of normal (ULN), except for i) patients with documented Gilbert's syndrome for whom any bilirubin value was allowed and ii) for patients with asymptomatic hyperbilirubinemia (liver transaminases and alkaline phosphatase within normal range).
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 x ULN.
- Serum lipase ≤ 2 x ULN
- Alkaline phosphatase ≤ 2.5 x ULN
- Serum creatinine <1.5 x ULN

8. Patients had the following electrolyte values ≥ lower limit of normal limits or corrected to within normal limits with supplements prior to the first dose of study medication:

- Potassium
- Magnesium
- Total calcium (corrected for serum albumin)

9. Patients had to have normal marrow function as defined:

- Absolute Neutrophil Count ≥ 1.5 x 109/L
- Hemoglobin ≥ 9.0 g/dL
- Platelets ≥ 100 x 109/L

10. Written informed consent was obtained prior to any screening procedures.

Exclusion criteria

Patients eligible for this study were not to meet any of the following criteria:

1. Prior AP, blast crisis (BC) or allo-transplant

2. Patient had a documented MR4.5 at the time when switching from imatinib to nilotinib

3. Patients with known atypical transcript. An atypical transcript was defined by the presence of any transcript in the absence of the major transcripts b3a2 (e14a2) and b2a2 (e13a2) or p210 protein.

4. CML treatment resistant mutation(s) (T315I, E255K/V, Y253H, F359C/V) detected by a testing done in the past (there was no requirement to perform mutation testing at study entry if it was not done in the past).

5. Dose reductions due to neutropenia or thrombocytopenia in the past six months.

6. Patient ever attempted to permanently discontinue imatinib or nilotinib treatment.

7. Known impaired cardiac function including any one of the following:

- Inability to determine the QT interval on electrocardiogram (ECG)
- 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 tachyarrhythmia
- Clinically significant resting bradycardia
- QTcF >480 ms
- History or clinical signs of myocardial infarction within one year prior to study entry
- History of unstable angina within one year prior to study entry
- Other clinically significant heart disease (e.g. uncontrolled congestive heart failure or uncontrolled hypertension)

8. Severe and/or uncontrolled concurrent medical disease that in the opinion of the Investigator caused unacceptable safety risks or compromised with being compliant to the protocol (e.g. uncontrolled diabetes (defined as HbA1c > 9%), uncontrolled infection).

9. History of acute pancreatitis, within one year prior to study entry or past medical history of chronic pancreatitis.

10. Known presence of a significant congenital or acquired bleeding disorder unrelated to cancer.

11. History of another active malignancy within five years prior to study entry with the exception of previous or concomitant basal cell skin cancer, previous cervical carcinoma in situ treated curatively.

12. Patients who had not recovered from prior surgery.

13. Treatment with other investigational agents (defined as not used in accordance with the approved indication) within four weeks of Day 1.

14. Patients actively receiving therapy with strong Cytochrome 3A4 (CYP3A4) inhibitors and/or inducers, and the treatment neither discontinued nor switched to a different medication prior to study entry..

15. Patients actively receiving therapy with herbal medicines that were strong CYP3A4 inhibitors and/or inducers, and the treatment was neither discontinued nor switched to a different medication prior to study entry. These herbal medicines included but not limited to Echinacea (including E. purpurea, E. angustifolia and E. pallida), Piperine, Artemisinin, St. John's Wort, and Ginkgo.

16. Patients who were receiving treatment with any medications that had the potential to prolong the QT interval and the treatment was neither safely discontinued nor switched to a different medication prior to study entry.

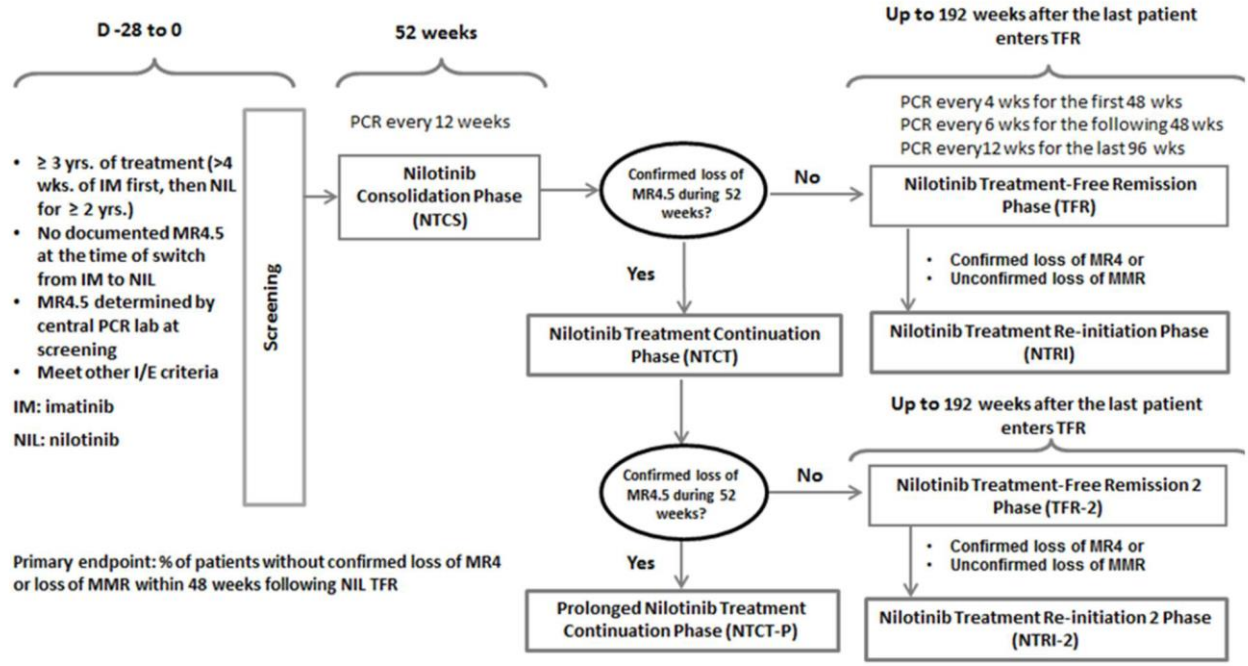
17. Impairment of gastrointestinal (GI) function or GI disease that might significantly alter the absorption of study drug (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or gastric bypass surgery).

18. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin laboratory test.

19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they had a negative serum pregnancy test before the initiation of the study and were using highly effective methods of contraception during the study and for 14 days after the final dose of nilotinib.

Treatments

Figure 4 Study design in Study A2408 (ENESTop)



Patients received the same nilotinib dose as they received prior to study entry.

Objectives/Outcomes/endpoints

The primary efficacy variable in Study A2408 was the proportion of patients without loss of MMR or confirmed loss of MR4 within 48 weeks following the start of the nilotinib TFR phase.

The main secondary efficacy endpoints assessed in the current analysis were:

- TFS after the start of the TFR phase
- MR4.5 rate at 48 weeks after start of the TFR phase
- Proportion of patients who regained MR4.5 and MR4 within the first 48 weeks of the NTRI phase

- Proportion of patients who regained MR4.5, MR4 and MMR within the first 48 weeks of the NTRI phase in patients who re-start treatment due to loss of MMR in the TFR phase
- Time required to regain MR4 and MR4.5 in patients who re-initiated treatment due to either confirmed loss of MR4 or loss of MMR in the TFR phase
- Time required to regain MMR, MR4 and MR4.5 in patients who re-initiated treatment due to loss of MMR
- PFS after the start of the TFR phase
- OS after the start of the TFR
- Kinetics of BCR-ABL/ABL transcript levels after restart of nilotinib treatment

The exploratory efficacy endpoints assessed in the current analysis are:

- Association between baseline demographics/disease history and primary endpoint
- Patient-reported outcomes and resource utilization
- BCR-ABL mutations in patients who lost MMR or confirmed loss of MR4 during the TFR phase.

Sample size

The study was designed with a 90% power to test the null hypothesis. The null hypothesis was that the rate of no documented confirmed loss of MR4, no loss of MMR and no re-initiation of nilotinib therapy in the first 48 weeks after nilotinib TFR was 10% or less with an alternative hypothesis that this rate is >10%.

The sample size was based on an exact test for single proportion to test the null hypothesis; H0: $p \leq 0.10$, where p was the rate of no documented confirmed loss of MR4, no loss of MMR and no re-initiation of nilotinib therapy in the first 48 weeks after nilotinib cessation. If the true rate $p \geq 0.25$, then with one-sided alpha level of 2.5% and a power of 90%, a minimum of approximately 70 patients were required to enter the TFR phase after the NTCS phase. Based on the results of the ENESTcmr study, approximately 30% of patients were to experience a loss of MR4.5 once it was achieved during the NTCS phase. Considering an additional 10% attrition rate, it was assumed that approximately 40% of the patients would not be eligible for TFR after 52 weeks of the NTCS phase. Thus, approximately 117 patients were to be enrolled into this study.

The study was expected to close at the earlier of the date on which 70 patients had entered the TFR phase or the date on which 117 patients had been enrolled in the NTCS phase. This study had enrolled 163 patients by 13-Dec-2013, the date when the patient enrollment was closed. With 163 patients enrolled, assuming approximately 40% of enrolled patients who had MR4.5 at study entry would not be eligible for starting the TFR phase, there were to be approximately 98 patients who entered TFR.

Assuming that the true rate of no documented confirmed loss of MR4, no loss of MMR and no re-initiation of nilotinib therapy in the first 48 weeks after nilotinib cessation was 25%, with a 10% rate for the null hypothesis, the study had a 97% power with 1-sided alpha level of 2.5% to test the null hypothesis. The power increased by 7% based on the 163 enrolled patients compared to the originally planned 90% power based on the 117 enrolled patients with all the other assumptions for the power calculation being the same.

Randomisation

Not applicable.

Blinding (masking)

This was an open-label study.

Statistical methods

The primary efficacy analysis was performed on the FAS. The primary endpoint (rate of successful TFR) was presented together with an exact 95% Clopper-Pearson confidence interval (CI). The null hypothesis was to be rejected if the lower limit of the 95% CI was greater than 0.10. The primary analysis was repeated on the PPS as a supportive analysis. All demographic data, medical history and current medical conditions at study start, and disease history were summarized and listed for the FAS and Safety set.

The rate of molecular responses by certain time points after starting the TFR phase as well as the rate of patients who re-achieved molecular responses (MR4.5/MR4/MMR) with nilotinib retreatment were presented together with an exact 95% Clopper-Pearson CI. Kinetics of BCR-ABL transcript levels after re-start of nilotinib therapy were presented by a box-plot of BCR-ABL ratio over time and were also summarized over time.

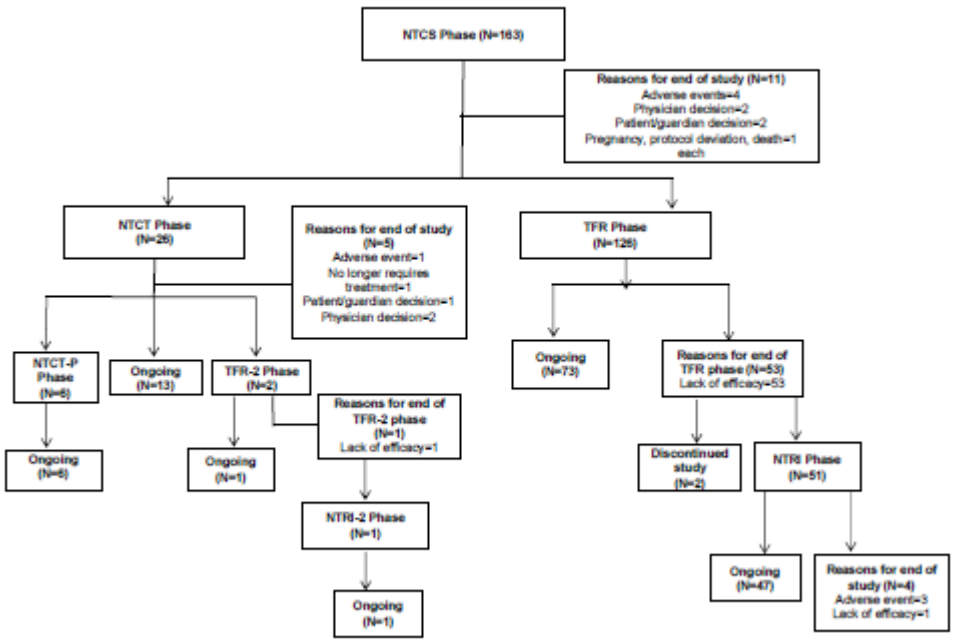
All time to event endpoints including duration of treatment re-initiation required to regain MMR, MR4 and MR4.5, TFS, PFS and OS were analyzed using the Kaplan-Meier (KM) method and were presented by KM plots.

All nilotinib concentrations were listed using the Safety set. The following is the list of analyses conducted to investigate the nilotinib concentration- efficacy relationship: Scatter plot of BCR ABL ratio (%) at 48 weeks of the NTCS phase vs. trough nilotinib concentration and the TFR phase entry status was summarized using contingency table by trough nilotinib concentration categories (by quartiles). Safety set was used for all safety analyses. Since the primary interest of the study was to assess the benefit of stopping treatment, particular analysis was performed on the patients who entered the TFR phase (TFR Safety set): those analyses focused on the differences of the incidence of safety events (AEs and lab abnormalities) between the NTCS phase and the first 48-weeks of the TFR phase to allow fair comparison

Results

Participant flow

Figure 5 Patient Disposition – Study A2408 (safety set)



Recruitment

First patient enrolled: 20-Dec-2012 (first patient first visit)

Last patient completed: study is ongoing.

Study centers: Argentina (2), Australia (3), Belgium (1), Brazil (6), Canada (4), France (5), Germany (5), Greece (3), Israel (3), Japan (7), Mexico (1), Poland (3), Russia (3), Singapore (1), South Korea (1), Spain (8), UK (2), US (5).

Conduct of the study

Protocol amendments

The study protocol was amended two times. The key features of each amendment are given below:

Amendment 1 (released on 07-Jul-2013): At the time of the amendment the study was in thestartup phase; 21 patients had been enrolled as of 25-June-2013.

Primary purpose for the amendment included but not limited to:

- To allow patient access to both clinical and commercial drug supply. Source of the drug supply was expected to change during the course of the study. However, all drug supply used in the study continued to be provided free to the patients by Novartis. In addition, protocol changes were implemented to address questions identified during the study startup as below:
- To clarify the pregnancy language to ensure consistency across all nilotinib clinical trials including instructions on how to deal with pregnancy during the TFR phases.
- Allowed for extension of screening window from 14 days to 28 days to allow more time for screening procedures.
- To clarify duration of imatinib therapy prior to switch to nilotinib.
- Allowed screening of patients from AMN107A2405 (ENESTcmr) or Study AMN107EIC01 (ENEST1st) study for participation in this study without having first to discontinue from either study. Patients would discontinue from these studies only if they were confirmed eligible for the current study AMN107A2408. This practice was in compliance with the International Conference on Harmonization (ICH) Topic E8 guidelines as it constituted a "justified exception one of which being that the patients in both these studies were treated and will continue to be treated with the same drug, nilotinib (Tasigna®), at the same dose/same formulation in the approved indication as in current study AMN107A2408.
- Allowed earlier re-screening of patients by reducing re-screening window from 12 weeks to approximately four weeks ± 7 days
- Clarification provided to ensure monitoring of AEs for 30 days after the last dose of study treatment or last day of the TFR/TFR-2 phase. In addition, SAEs were to be followed until clinical improvement, resolution, or stabilization.
- Biomarker and pharmacogenetics sections were included
- Study title was updated to include the pathology (CML added) of study population.
- Information added to the definition of adequate end organ function for direct bilirubin
- Clarification was provided to serious adverse event (SAE) reporting regarding safety assessment

Amendment 2 (11-Aug-2014): At the time of this amendment, 163 patients were screened for enrollment as of December 2013

The main purposes of the amendment were:

- To include cholesterol testing in the assessment schedule. Elevations in total serum cholesterol and low density lipoprotein cholesterol was observed very commonly (more than 10%) in patients treated with nilotinib and commonly (between 1 to 10%) in patients treated with imatinib. Most of the cholesterol elevations were grade 1 (>ULN - 300 mg/dL; >ULN - 7.75 mmol/L) or 2 (>300 – 400 mg/dL; >7.75 - 10.34 mmol/L), and some elevations were present prior to initiation of CML therapy. Lipid profiles including total cholesterol, LDL-C and HDL-C were assessed during the conduct of this study. If test results warranted intervention, Investigators followed their local standards of practice or treatment guidelines which recommended treatment even for grade 1 cholesterol elevation. Before prescribing a lipid-lowering medication, the possibility of drug-drug interactions was considered due to moderate inhibitory effect of nilotinib on CYP3A4 isoenzyme that was involved in the metabolic pathway of some statins (Hydroxy Methyl-Glutaryl-Coenzyme A reductase inhibitors).
- To provide a harmonization on dose reductions guidelines across Novartis-sponsored nilotinib study protocols. Hence the dose reduction guidelines for the following non-hematologic toxicities were updated:
- Hepatobiliary
- Ischemic cardiovascular evaluation for grade 2 and above to Hold therapy and refer patient for assessment; patients with grade 2 resumed treatment at lower dose on event improving to grade 1and patients with grade 3/4 discontinued treatment.
- Pancreatitis grade 4: change from "Hold therapy" to "Stop therapy".
- Cardiac QTcF prolongation to include instructions for Investigator to follow local guidelines for management of QTcF.
- Cardiac "Other": change from "Hold therapy" to "Stop therapy".
- To incorporate guidance for the management of:
- Serum cholesterol increased.
- Blood glucose increased.
- Other cardiac risk factors.
- Ischemic vascular or ischemic cardiovascular events occurring in patients treated with nilotinib.
- To incorporate precaution of use for antacid drugs to be aligned with Tasigna® Food and Drug Administration Prescribing Information and European Medicines Agency SmPC.
- To define ischemic vascular and ischemic cardiovascular events as AEs of special interest, and their reporting.
- The duration of the TFR phase was clarified to be up to 192 weeks after the last patient enters TFR throughout the protocol.
- Modifications to clarify the biomarker assessments
- To clarify the specification of the statistical alternative hypothesis H1.

- To inform the IRBs/IECs/REBs and HAs about over-recruitment and its impact on the stopping rules applied to the first 48 weeks after start of TFR and on the sample size calculation.
- To clarify the biochemistry laboratory parameter for calcium
- Modification of the Pharmacokinetic endpoint and corresponding PK blood collection log
- Retrospective Sokal risk score collection was included
- To correct discrepancies and add clarifications within the protocol.

Changes in planned analysis

The original report and analysis plan (RAP Module 3) was finalized and approved on 30-June-2014, which was aligned (including protocol amendment 1).

The RAP Module 3 was amended (Amendment 1) on 25-Sep-2015 before the database lock for the primary analysis, with the following main changes in the planned analysis:

- Added analysis description for the exploratory analyses to identify potential predictive factors for successful TFR;
- Updated reporting of deaths describing causes of deaths (and not only number of deaths) post study discontinuation in the Survival follow-up period;
- Added analysis to assess patient proportions who had MR4.5 at 48 weeks without reinitiation of nilotinib therapy, after starting the TFR phase.

The RAP Module 3 was amended (Amendment 2) on 31-Jan-2016 before the database lock for the primary analysis, with the following main changes in the planned analysis:

- Clarified that in analyses comparing consolidation to TFR, only the first year of TFR was taken into account to allow fair comparison between the 2 periods;
- Removed the EQ-5D-5L health index score from planned CSR analyses as it would not be relevant to compute it for the entire study population, but rather only if needed for a specific country/region population and adapted to this particular country/region;
- Modified the criteria of evaluable PK trough samples for the PAS according to PK dosing and sampling date/time;
- Acknowledged the fact that the Sokal risk score data may not be available for a significant proportion of patients at the time of primary analysis and that it may not allow evaluating the impact of Sokal risk group on the primary endpoint;
- Clarified that a patient with a detectable p190 BCR-ABL transcript or any other minor BCR-ABL transcript (any atypical transcript for CML patients, different than the p210 major BCR-ABL transcript which is the typical transcript for the CML patients) are considered as a non-responder at all time-points in the study.
- The RAP Module 3 was amended (Addendum 1) on 22-Mar-2016 after the database lock for the primary analysis, with the following main changes in the planned analysis:
- Correct the formulas for calculating the severity score and interference score for MDASI-CML.
- Added exploratory analyses to further characterize the AE grouping musculoskeletal pain. The protocol mentions that PFS on study including the survival follow-up period and OS will be determined separately in patients who did not enter the TFR phase. However, this analysis was not included in the RAP as the main focus is for patients who entered the TFR phase. In

addition, this analysis is irrelevant as no patients progressed and only one patient died, in the NTCS phase.

Protocol deviations

Deviations occurred in all phases of the Study A2408 are summarized in Table 14.

Table 14 Protocol deviations in all phases Study A2408 (safety Set)

Protocol deviation	All N=163 n=(%)
Any protocol deviation	
-Total	105 (64.4)
Any major protocol deviation	
-Total	5 (3.1)
Patient received a TKI besides imatinib and nilotinib since initial CML diagnosis and prior to study entry.	2 (1.2)
Presence of transcript type in the absence of b3a2 (e14a2) and b2a2 (e13a2) or p210 protein from MMD report since screening[1]	1 (0.6)
Patient had atypical transcript prior to study entry[2]	1 (0.6)
Patient has a history of other active malignancy within 5 years prior to study entry other than previous or concomitant basal cell skin cancer, previous cervical carcinoma in situ treated curatively	1 (0.6)
Any minor protocol deviation	
-Total	104 (63.8)
Bone marrow assessment was not performed when a patient has loss of MMR, or when a patient's BCR-ABL ratio has risen to >1% IS (equivalent to loss of CCyR), or when a patient has a loss of CHR.	33 (20.2)
Administration of QT prolonging agents	28 (17.2)
PCR assessment not performed (except Visit 778/201, Visit 781/401 and during prolonged treatment continuation phase)	20 (12.3)
No ECG performed before restart of nilotinib and/or every 48 weeks while on nilotinib treatment	19 (11.7)
Patient biochemistry lab value not met requirement	12 (7.4)
The female patient did not perform home urine pregnancy test	9 (5.5)
Patient receive treatment with any medications that have the potential to prolong QT interval and the treatment cannot be safely discontinued or switched to a different one prior to study entry.	8 (4.9)
The patient did not re-start nilotinib treatment at 300 mg bid or 400 mg bid	8 (4.9)
Study medication noncompliance	7 (4.3)
Study medication was not 300 mg bid, 400 mg bid or 400 mg qd at baseline	6 (3.7)
Administration of strong CYP3A4 inducer and inhibitor	4 (2.5)
Patient entered the study on a reduced dose that was not considered permanently reduced for 6 month prior to study entry	4 (2.5)
Female patient of child bearing potential is not using highly effective contraception during the study[3]	3 (1.8)
No ECG performed at screening	3 (1.8)
Use of nilotinib from other study or commercial supply[4]	2 (1.2)
Study medication dose above 400 mg bid during the conduct of the study	2 (1.2)
Patient has impaired cardiac function	2 (1.2)
The patient missed 1 dose of study medication in the 8 days prior to PK sample collection	2 (1.2)
Performance status not met	1 (0.6)
Study drug not appropriated adjusted as per protocol	1 (0.6)
Patient became pregnant[5]	1 (0.6)

CML= Chronic myeloid leukemia, ECG = electrocardiogram, GCP = good clinical practice, MMD = MolecularMD MRDx™ BCR-ABL Test, PCR = polymerase chain reaction
A patient may have multiple protocol deviations.

Baseline data

Table 15 Demographic characteristics –study A2408 (FAS)

Demographic variable	All N=126
Age (years)	
n	126
Mean (SD)	55.0 (14.28)
Median	56.0
25th - 75th percentile	46.0 - 65.0
Min - Max	21-86
Age category (years) -n (%)	
<35	12 (9.5)
≥ 35 - <45	18 (14.3)
≥ 45 - <55	27 (21.4)
≥ 55 - <65	34 (27.0)
≥ 65	35 (27.8)
Sex -n (%)	
Male	56 (44.4)
Female	70 (55.6)
Race -n (%)	
Caucasian	97 (77.0)
Black	3 (2.4)
Asian	19 (15.1)
Native American	1 (0.8)
Other	6 (4.8)
Ethnicity -n (%)	
East Asian	16 (12.7)
Hispanic or Latino	25 (19.8)
Southeast Asian	1 (0.8)
West Asian	2 (1.6)
Russian	7 (5.6)
Mixed Ethnicity	5 (4.0)
Not Reported	11 (8.7)
Other	48 (38.1)
Unknown	11 (8.7)
ECOG performance status - n (%)	
0	107 (84.9)
1	18 (14.3)
Missing	1 (0.8)

ECOG = Eastern Cooperative Oncology Group
Demographic characteristics at study entry.

Table 16 Disease history –Study A24008 (FAS)

Characteristic	All N=126
Time since initial diagnosis of CML until study entry (months)	
n	126
Mean (SD)	86.9 (43.73)
Median	77.9
25th - 75th percentile	53.0 - 104.9
Min - Max	37-268
Time since achievement of MR4.5 on nilotinib until study entry (months)	
n	126
Mean (SD)	23.4 (18.92)
Median	19.8
25th - 75th percentile	7.3 - 34.3
Min - Max	0-78
PCR result at the time of switching from imatinib to nilotinib -n (%)	
Not reaching MR 4.5	92 (73.0)
Unknown	34 (27.0)
Atypical transcript -n (%)	
Yes	0
No	126 (100)
Sokal risk score at diagnosis -n (%)	
High	12 (9.5)
Intermediate	19 (15.1)
Low	43 (34.1)
Missing	52 (41.3)

Table 17 Antineoplastic treatment with a TKI before TFR phase – Study A2408 (FAS)

Characteristic	All N=126
Duration of TKI treatment prior to the TFR phase entry (months)	
N	126
Mean (SD)	91.13 (30.608)
Median	87.67
Min – Max	48.9-170.5
Duration on nilotinib treatment prior to the TFR phase entry (months)	
N	126
Mean (SD)	57.85 (17.351)
Median	52.98
Min – Max	36.5-108.6
Daily dose of nilotinib prior to the TFR phase entry (mg) – n (%)	
300	1 (0.8)
400	21 (16.7)
450	1 (0.8)
600	37 (29.4)
800	66 (52.4)

Numbers analysed

Table 18 Analysis set by study phase (safety set)

Analysis population	NTCS phase N=163 n (%)	TFR phase N=126 n (%)	NTRI phase N=51 n (%)	NTCT phase N=26 n (%)	TFR-2 phase N=2 n (%)	NTRI-2 phase N=1 n (%)	NTCT-P phase N=6 n (%)
Full Analysis Set	NA	126 (100)	NA	NA	NA	NA	NA
Safety set[1]	163 (100)	126 (100)	51 (100)	26 (100)	2 (100)	1 (100)	6 (100)
Per Protocol Set	NA	122 (96.8)	NA	NA	NA	NA	NA
Pharmacokinetic Analysis Set	70 (42.9)	NA	NA	NA	NA	NA	NA

NTCS=nilotinib treatment consolidation; TFR=treatment-free remission; NTCT=nilotinib treatment continuation; NTRI=nilotinib treatment re-initiation; NTCT-P=nilotinib treatment prolonged continuation
N is the number of patients who entered the study phase.
[1] Patients are summarized according to study phases

Outcomes and estimation

Primary endpoint: No loss of MMR or confirmed loss of MR4 within 48 weeks

Table 19 Proportion of patients without loss of MMR or confirmed loss of MR4 within 48 weeks after starting the TFR phase – Study A2408 (FAS)

	TFR Phase N=126	
	n (%)	95% CI
Responder	73 (57.9)	(48.8, 66.7)

TFR=treatment-free remission
The 95% CI for the frequency distribution was computed using exact Clopper-Pearson method.

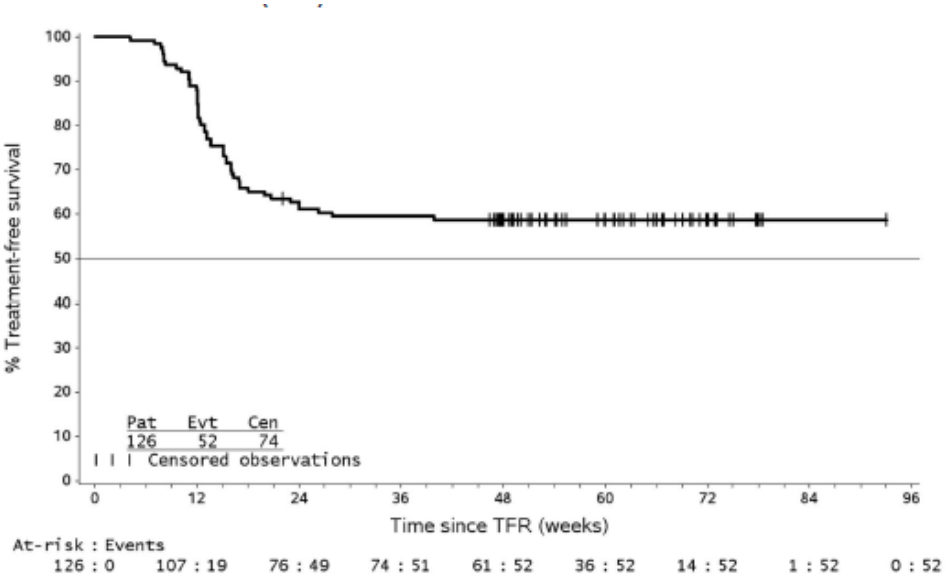
Secondary endpoint – TFS after the start of TFR phase

Table 20 TFS estimates after the start of the TFR phase – Study A2408 (FAS)

Category	TFR phase N=126
Number of events – n (%)	52 (41.3)
Number censored – n (%)	74 (58.7)
Percentiles (95% CI) (weeks)	
25th percentile	15.1 (12.1 - 16.9)
Median	NE (39.9 - NE)
75th percentile	NE (NE)
Kaplan-Meier estimate (95% CI)	
4 weeks	100 [100 , 100]
8 weeks	96.0 [90.7, 98.3]
12 weeks	84.9 [77.4, 90.1]
16 weeks	69.8 [61.0, 77.0]
20 weeks	64.3 [55.3, 72.0]
24 weeks	61.1 [52.0, 69.0]
36 weeks	59.5 [50.4, 67.5]
48 weeks	58.7 [49.6, 66.7]

NE: Not estimable

Table 21 Kaplan-Meier estimates of TFS after the start of the TFR phase – Study A2408 (FAS)



Secondary endpoint – MR4.5 rate at 48 weeks after start of the TFR phase

Table 22 MR 4.5 rate at 48 weeks after starting the TFR phase with retreated patients counted as non-responders –Study A2408 (FAS)

	TFR Phase N=126	
	n (%)	95% CI
Week 48		
Responder	67(53.2)	(44.1, 62.1)

The 95% CI is computed using exact Clopper-Pearson method.

Secondary endpoint – Proportion of patients who regained MR4.5 and MR4 within the first 48 weeks of the NRTI phase

Table 23 Proportion of patients who regained MR4.5 and MR4 within the first 48 weeks of the NTRI phase – Study A2408 (NTRI Safety Set)

	NTRI phase N=51	
	n (%)	95% CI
MR4.5	47 (92.2)	(81.1, 97.8)
MR 4	48 (94.1)	(83.8, 98.8)

NTRI=nilotinib treatment re-initiation
The 95% CI for the frequency distribution was computed using exact Clopper-Pearson method.

Secondary endpoint: Proportion of patients who regained MR4.5, MR4 and MMR within the first 48 weeks of the NTRI phase in patients who re-start treatment due to loss of MMR in the TFR phase

Table 24 Proportion of patients who regained MR4.5, MR4 and MMR within the first 48 weeks of the NTRI phase in patients who re-started treatment due to loss of MMR in the TFR phase – Study A2408 (NTRI Safery set)

	NTRI phase N=51	
	n (%)	95% CI
Number of patients with treatment re-initiation due to loss of MMR in the TFR phase	34 (66.7)	
MR4.5[1]	30 (88.2)	(72.5, 96.7)
MR4[1]	31 (91.2)	(76.3, 98.1)
MMR[1]	33 (97.1)[2]	(84.7, 99.9)

NTRI=nilotinib treatment re-initiation
[1] The percentages of patients who achieve MR4.5, MR4 and MMR is based on the 'number of patients with treatment re-initiation due to loss of MMR in the TFR phase'

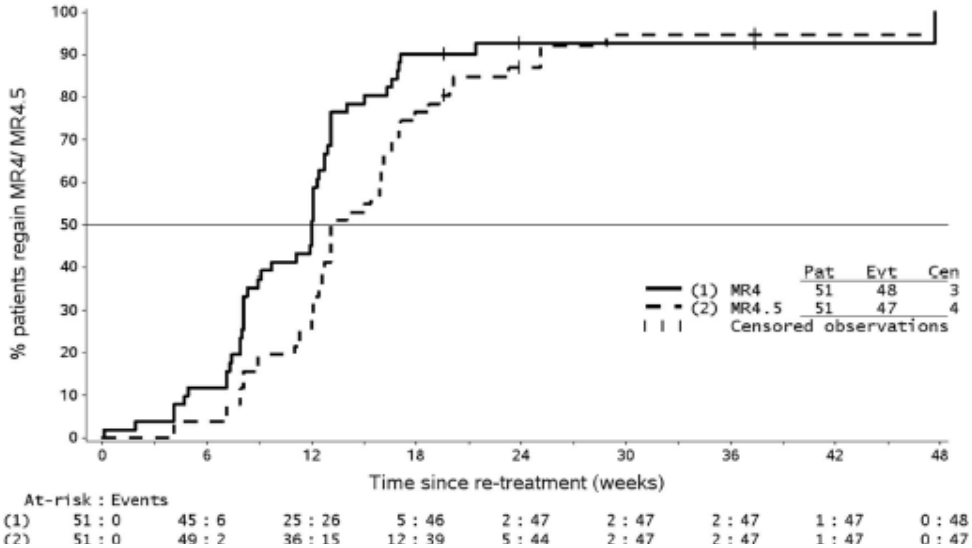
Secondary endpoint: Time required to regain MR4 and MR4.5 in patients who re-initiated treatment due to either confirmed loss of MR4 or loss of MMR in the TFR phase

Table 25 Time required to regain MR4 and MR4.5 in patients who re-started treatment due to loss of MMR or confirmed loss of MR4 in the TFR phase – Study A2408 (NTRI Safety Set)

Category	NTRI Phase N = 51
Regain MR4	
Number of events – n (%)	48 (94.1)
Number censored – n (%)	3 (5.9)
Percentiles (95% CI) (weeks)	
25th percentile	8.0 (7.1-8.9)
Median	12.0 (8.3-12.7)
75th percentile	13.1 (12.4-16.9)
Kaplan-Meier estimate (95% CI)	
4 weeks	3.9 [1.0,14.8]
8 weeks	25.5 [15.7,39.8]
12 weeks	51.0 [38.2,65.2]
16 weeks	80.4 [68.6,89.9]
20 weeks	90.2 [80.3,96.4]
24 weeks	92.6 [83.1,97.8]
36 weeks	92.6 [83.1,97.8]
48 weeks	100 [NE]
Regain MR4.5	
Number of events – n (%)	47 (92.2)
Number censored – n (%)	4 (7.8)
Percentiles (95% CI) (weeks)	
25th percentile	11.3 (8.1-12.6)
Median	13.1 (12.4-16.1)
75th percentile	17.9 (16.0-23.3)
Kaplan-Meier estimate (95% CI)	
4 weeks	[NE]
8 weeks	11.8 [5.5,24.3]
12 weeks	29.4 [18.9,44.0]
16 weeks	62.7 [49.8,75.7]
20 weeks	82.6 [71.0,91.5]
24 weeks	86.9 [76.0,94.5]
36 weeks	94.8 [85.1,99.0]
48 weeks	94.8 [85.1,99.0]

NTRI=nilotinib treatment re-initiation
NE: Not estimable

Table 26 Kaplan- Meier plot of time required to regain MR4/MR4.5 in treatment re-initiation phase after either confirmed loss of MR4 or loss of MMR in TFR phase- Study A2408 (NTRI Safety set)



Secondary endpoint: PFS

As of the data cut-off date, none of the 126 patients in the TFR phase had a PFS event (progression to AP/BC or death) and all patients were censored for PFS analysis

Secondary endpoint: OS

As of the data cut-off date, all of the 126 patients in the TFR phase were alive.

Ancillary analyses

Association between baseline demographics/disease history and primary endpoint

Analysis of predictors for successful TFR is defined according to the primary endpoint definition (no loss of MMR or confirmed loss of MR4 by 48 weeks of TFR). Various analyses were done to evaluate the impact of potential predictive factors on the primary endpoint, in the FAS population, for all patients who entered the TFR phase. In the patients who entered the TFR phase (FAS), between study entry and entry in the TFR phase, there is by protocol a fixed duration of 52 weeks during which all patients in FAS had to remain on nilotinib treatment and maintained MR4.5 before entering in the TFR phase. This means that the effect of 1) the duration of prior TKI treatment up to study entry, and 2) of the time from the first MR4.5 up to the time of study entry on whether successful TFR occurred is equivalent to the eff ect reported up to the time of TFR entry. Therefore, the conclusions regarding the impact of these factors as analyzed up to study entry can be transposed to that of the same factors up to TFR entry.

- Multivariate logistic regression analysis for successful TFR with age, gender, duration of prior TKI treatment, time to first MR4.5 on nilotinib prior to study entry, time since first MR4.5 until study entry, and starting dose level in the consolidation phase as explanatory variables, did not provide evidence of strong predictors of successful TFR.
- The Stepwise selection model (with level of 0.1 for both variable entry and stay) selected gender (odds ratio 0.523 [95% CI: 0.251, 1.087]) and time since MR4.5 until study entry (odds ratio 1.019 [95% CI: 0.999, 1.040]) as the 2 factors most correlated with successful

TFR, but for both of them, the CI for the odds ratio included one and they are not considered as clear predictive factors.

- The median duration on TKI treatment prior to study entry was similar in patients who had successful TFR vs patients who did not have successful TFR (74.5 vs 75.9 months).
- The median duration on nilotinib treatment prior to study entry was higher in patients who had successful TFR vs patients who did not have successful TFR (44.9 vs 36.1 months). Similarly, the time since first achievement of MR4.5 until study entry was higher in patients who had successful TFR vs patients who did not have successful TFR (27.10 vs 17.20 months).

There was no notable difference in baseline demographics, disease, and prior treatment or prior response characteristics between patients who had successful TFR and patients who did not have successful TFR.

STUDY A2405 (ENESTcmr)

This study was already assessed in detail in an earlier variation procedure (EMEA/H/C/00798/II/0061) and thus, discussion focus only one main issues relevant for this application. Overall, this study adds no further data on the discontinuation issue and thus, supportive value is only low.

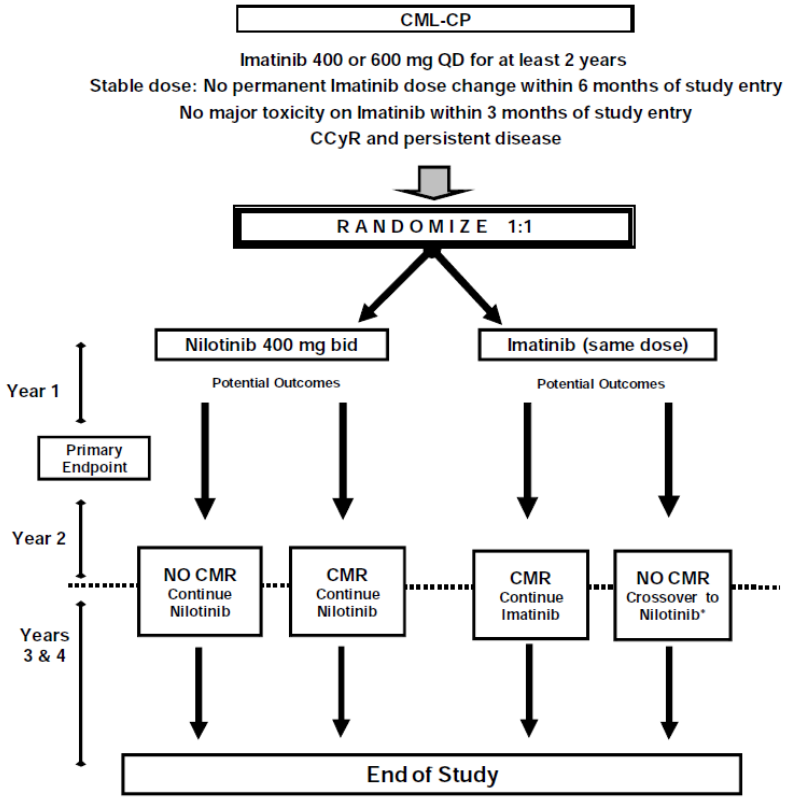
For these reasons study ENESTcmr will not be re-assessed, but high-level results will be provided.

Study A2405 (ENESTcmr) was an open label, randomized study of nilotinib vs. standard imatinib conducted between 2009 and 2012 in adult patient with CML-CP. The primary objective of the study was to compare the rate of confirmed best cumulative CMR within the first year of study therapy with nilotinib or imatinib. Furthermore, this trials aims to assess the kinetics of CMR achieved and to compare PFS in both treatment arms as key secondary endpoints. This study was assessed and discussed extensively already during a previous procedure in 2014 (EMEA/H/C/00798/II/0061). Therefore, only a short summary is provided here. The dose and schedule used (400 mg bid) was consistent with the approved second-line indication.

Patients initially randomized to imatinib were offered the opportunity to crossover to nilotinib therapy following treatment failure (loss of CCyR, loss of MMR, or progression to AP/BC), or 2 years after CMR had not been attained. No crossover was provided for patients randomized to the nilotinib arm.

Yearly updates of the efficacy and safety results were planned for the duration of the study. The efficacy data presented in the submission is up to 48 months which was marking the end of the treatment period by protocol.

Figure 6 Study design



*Cross-over from imatinib to nilotinib was permitted only at the end of year 2 for patients without CMR

The secondary endpoints were to be tested at the 5% significance level, only when the primary endpoint was significant at the 5% level. As the primary endpoint was not significant, for the secondary efficacy endpoints reported, p-values are provided for descriptive purposes only and were not adjusted for multiple comparisons. The rate of the CMR at Month 6, 12, 18, and 24 during the first two years of treatments and the rate of confirmed best cumulative CMR by month 24 and the rate of maintained CMR at Month 12 and 24 were presented along with the 95% confidence interval by treatment groups.

The primary endpoint was the rate of confirmed best cumulative CMR during first 12 months. The rate of confirmed best cumulative CMR during the first 12 months was 12.5% in the nilotinib arm and 5.8% in the imatinib arm. The study did not meet the primary endpoint as the p-value for the two-sided CMH test was p=0.1083, which was above the required significance level of 0.05. However, with an odds ratio (OR) of 2.096 in favor of nilotinib, these results were suggestive of the potential clinical benefit associated with nilotinib in this patient population.

A 2-sided stratified Cochran-Mantel-Haenszel (CMH) test was used to test the null hypothesis (of no difference in the rate of confirmed best cumulative CMR between treatment arms) at the 0.05 significance level.

Table 27 Rate of confirmed best cumulative CMR during the first 12 months (ITT) – Study A2405

	Nilotinib	**Imatinib**
Category	**N=104**	**N=103**
Responder, n (%)	13 (12.5)	6 (5.8)
Non-responder, n (%)	91 (87.5)	97 (94.2)
95% CI of response rate	6.83, 20.43	2.17, 12.25
Odds ratio (nilotinib vs. imatinib) with (95% CI)[1]	2.096 (0.766, 5.738)	
P-value from CMH test[2]	0.1083	

[1]Odds Ratio is adjusted for prior imatinib treatment and interferon use.
[2]Cochran-Mantel-Haenszel test is stratified by prior imatinib treatment and interferon use.

The insufficient difference between the two treatment groups and lack of statistical significance at the early 12-month time point was attributed to the kinetics of molecular response which could not have been accurately predicted at the time of the study conception/design.

In accordance with the predefined statistical procedure described in the protocol, the secondary endpoints would only formally be tested at the two-sided α-level of 0.05 if the primary analysis reached statistical significance at Month 12. As the primary efficacy endpoint did not attain statistical significance, all other endpoints reported in the clinical study report were presented with nominal p-values, unadjusted for multiplicity, which are not reported here.

Longer-term follow-up of the primary endpoint provided compelling results at the 24-month analysis with an odds ratio of 2.103 (95% CI: 0.932, 4.742) and rates of confirmed CMR were 23.1% and 10.7%, respectively for the nilotinib and imatinib arms. Given the kinetics of molecular response, this analysis provides a more appropriate assessment of the two treatments under evaluation than the primary efficacy endpoint up to Month 12 [Study A2405 Table 14.2-5.4]. By 36 and 48 months, considering the responses up to crossover, nilotinib continued to have a higher number of patients achieving these deep molecular responses relative to continuing treatment.

Confirmed best cumulative CMR and unconfirmed MR4.5 (ITT)

The below analysis followed intent-to-treat (ITT) principle, i.e., even if patients achieved response only after crossover from imatinib to nilotinib, the response was credited to the arm to which they were randomized (imatinib). In line with the study design, it impacts results from Month 36 and 48 time points, where the difference between treatment arms tends to diminish because of patients originally randomized to imatinib who improved after switching to nilotinib.

Rates of confirmed best cumulative CMR up to Month 24 were 23.1% and 10.7%, respectively, for the nilotinib and imatinib treatment arms, with an OR of 2.103 (95% CI: 0.932, 4.742).

Rates of confirmed best cumulative CMR up to 36 months were 27.9% and 20.4%, for the nilotinib and imatinib arms, respectively, with an OR of 1.458 (95% CI: 0.754, 2.821). Rates of confirmed best cumulative CMR up to 48 months were 30.8% and 20.4%, for the nilotinib and imatinib arms, respectively, with an OR of 1.660 (95% CI: 0.869, 3.171).

The rate of best cumulative MR4.5 by Month 24 was 45.2% in the nilotinib arm and 24.3% in the imatinib arm (OR=2.682, 95% CI: 1.436, 5.009), by Month 36 the rates were 49.0% and 38.8% respectively, and by Month 48 the rates were 53.8% and 44.7%, respectively.

For patients who were not known to have CMR at baseline, the rates of unconfirmed CMR by 24 month were 32.7% and 18.0%, respectively, for the nilotinib and imatinib treatment arms, by Month 36 the rates were 40.6% and 31.0%, respectively, and by Month 48 the rates were 44.6% and 33.0%, respectively.

For patients who were without MR4.5 at baseline, the rate of unconfirmed MR4.5 by 24 months on study was 42.9% in the nilotinib arm and 20.8% in the imatinib arm, by Month 36 the rates were 46.9% and 36.5%, respectively, and by Month 48 the rates were 52.0% and 41.7%, respectively.

Confirmed CMR and unconfirmed MR4.5 up to crossover

On or before the 48-month PCR assessment, a total of 46 patients in the imatinib arm crossed over to nilotinib. Considering imatinib patients who achieved confirmed CMR for the first time after the crossover to nilotinib as non-responders to imatinib, the rate of best cumulative confirmed CMR up to 48 months was 30.8% in the nilotinib arm and 11.7% in the imatinib arm (OR=3.069; 95% CI: 1.450, 6.495).

Out of 46 crossed over patients, 9 patients (19.6%) achieved confirmed CMR for the first time after crossover to nilotinib.

The rate of cumulative unconfirmed MR4.5 up to 48 months (up to cross-over) was 53.8% in nilotinib arm and 32.0% in the imatinib arm (OR=2.578; 95% CI: 1.442, 4.607).

The rate of cumulative unconfirmed CMR up to crossover was 46.2% in nilotinib arm and 21.4% in the imatinib arm (OR=3.313; 95% CI: 1.773, 6.192).

Cumulative molecular response up to cross-over by baseline molecular response status showed that a higher proportion of patients in nilotinib arm achieved various levels of response compared to imatinib arm, when patients did not have the corresponding level of response at baseline Table 4-6.

Table 28 Cumulative molecular response rate up to cross-over by baseline molecular response status by Month 48 (ITT) – Study A2405

	Nilotinib N=104 n (%)	Imatinib N=103 n (%)
Number of patients known to have MMR at baseline	79 (76.0)	74 (71.8)
Number of patients not known to have MMR at baseline	24 (23.1)	28 (27.2)
MMR by 12 months	18 (75.0)	10 (35.7)
MMR by 24 months	20 (83.3)	14 (50.0)
MMR by 36 months	21 (87.5)	15 (53.6)
MMR by 48 months	21 (87.5)	15 (53.6)
MR4.5 by 48 months	8 (33.3)	1 (3.6)
CMR by 48 months	7 (29.2)	1 (3.6)
Number of patients known to have MR4.5 at baseline	5 (4.8)	6 (5.8)
Number of patients not known to have MR4.5 at baseline	98 (94.2)	96 (93.2)
MR4.5 by 12 months	32 (32.7)	13 (13.5)
MR4.5 by 24 months	42 (42.9)	20 (20.8)
MR4.5 by 36 months	46 (46.9)	25 (26.0)
MR4.5 by 48 months	51 (52.0)	27 (28.1)
CMR by 48 months	44 (44.9)	18 (18.8)
Number of patients known to have CMR at baseline	2 (1.9)	2 (1.9)

	Nilotinib N=104 n (%)	Imatinib N=103 n (%)
Number of patients not known to have CMR at baseline	101 (97.1)	100 (97.1)
CMR by 12 months	21 (20.8)	10 (10.0)
CMR by 24 months	33 (32.7)	18 (18.0)
CMR by 36 months	41 (40.6)	20 (20.0)
CMR by 48 months	45 (44.6)	20 (20.0)

Progression-free survival

Two patients (1.9%) in the nilotinib treatment arm and one patient (1.0%) in the imatinib arm had a PFS event. In the nilotinib arm, one patient died due to acute myocardial infarction, another patient died due cardiopulmonary failure and in the imatinib arm one patient died due to prostate cancer with bone metastasis [Study A2405-Table 14.2-2.4.1.1].

No patients progressed to AP/BC. No PFS events were reported after crossover.

Event-free survival (EFS)

A total of 17 patients experienced an EFS event (loss of CCyR, loss of MMR or death), with a higher number in the imatinib arm (10 patients) compared to the nilotinib arm (7 patients). Of these patients, five patients experienced loss of MMR and two patients died in the nilotinib arm. In the imatinib arm, the observed EFS events (up to crossover) were loss of MMR (four patients), loss of CCyR (three patients) and death (one patient) and two patients experienced loss of MMR following crossover [Study A2405-Table 14.2-3.2.2]. The reasons for deaths in both arms are explained in the PFS description.

Overall survival

Three patients (2.9%) in the nilotinib arm and three patients (2.9%) in the imatinib arm died during the study [Study A2405-Table 14.2-2.6.1].

Time to achievement of response

Kaplan-Meier estimate of median time to achievement of response was consistently earlier for the patients in the nilotinib arm (MR4.5: 24 months, 95% CI: 14.8, 47.5; CMR: 38.5 months, 95% CI: 26.3, 49.2), while in the imatinib arm the KM estimate of median time to achieve MR4.5 and CMR was 49.0 months (95% CI: 34.3, 49.0) and 49.0 months (NA, NA), respectively [Study A2405-Table 14.2-3.2.1], [Study A2405-Figure 14.2-3.1.3], and [Study A2405-Figure 14.2-3.1.1].

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Both the ENESTfreedom and the ENESTop studies are single-arm phase II studies in CML-CP patients.

ENESTfreedom was a multicentre phase II, single-arm, multi-center nilotinib TFR study in patients with BCR-ABL1 positive CML-CP, who had achieved durable minimal residual disease (MRD) status on first-line nilotinib treatment. The primary objective was to determine the percentage of patients who were in MMR at 48 weeks after starting the TFR phase. The inclusion/exclusion criteria clearly defined a patient population suitable for this study. Patients were treated with 300 mg bid or 400 mg once daily in case of tolerability issues, which is in line with clinical practice, however most of the patients were treated with 300 mg bid. The protocol amendments and changes in the planned analyses are few and minor; none of them was considered critical. The median age was 55 year and only 20% of the patients are above 65 years. The majority of the patients were Caucasian, ECOG 0 or 1. Only one patient was ECOG 2. The majority of the patients had a missing Sokal risk score, which was collected retrospectively after protocol amendment 3. In conclusion, the baseline characteristics showed a well-treated, fit and relatively young patient population.

The ENESTop was a phase II, single-arm, open- label study of TFR in CML-CP patients after achieving sustained MR4.5 on nilotinib. The inclusion criteria defined a patient population that had received at least 4 weeks of initial therapy with imatinib, and then switched to nilotinib for at least 2 years. Patients must have been treated with a TKI for at least 3 years. Patients with a confirmed MMR4.5 prior switch to nilotinib were excluded. Patients were not to have documented MR4.5 at the time of switch from imatinib to nilotinib. The primary objective was to evaluate the proportion of patients without loss of MMR or confirmed loss of MR4 within 48 weeks following nilotinib cessation. The MAH had defined one primary and several secondary and exploratory endpoints. The cut-off level in relation the primary endpoint was 10%. The protocol amendments and changes in the planned analysis were not considered critical. There were only few critical protocol deviations. The median age was 56 year and only 27% of the patients are above 65 years. The majority of the patients are Caucasian, ECOG 0 or 1. The Sokal risk score, which was collected retrospectively after protocol amendment, was missing in 41.3%. In conclusion, the baseline characteristics showed a well-treated, fit and relatively young patient population. The median duration of imatinib treatment prior to nilotinib treatment was 23.5 months in the ENESTop study, ie. almost 2 years.

Efficacy data and additional analyses

ENESTfreedom

The primary endpoint was not met, thus the study in principle failed due to a lower limit of the 95%CI below the 50% cut-off. However, as seen in relation to the secondary endpoints, several interesting observations were made. A large proportion of the patients maintained a deep molecular response (MMR4.5), and about 50% of the patients never relapsed suggesting a potential for cure. If relapse occur, it occurred within 24 weeks in the majority of the patients. When relapsed patients are re-treated, 98.8% of them regained MMR by 24 weeks. This is reassuring. PFS and OS data are immature.

ENESTop:

The study met its primary objective, showing TFR of 57.9%, where the 95%CI is 48.85-66.7%. The MAH has chosen 10% as the reference value above which the lower limit of the 95% CI had to be, which is lower than the cut-off level in the ENESTfreedom study (50%), however, since the aim in this study is "no documented loss of MR4, no loss of MMR" the lower cut-off is justified. The majority of patient that enter TFR phase, but eventually relapse, do so within 24 weeks. About 50% of patients continue to be in the TFR phase for more than 90 weeks. This is very interesting from a clinical perspective.

The majority of patients regained MR4 and MR4.5 within 24 weeks, and by 48 weeks 100% of the patients have regained MR4 and 94.8% have regained MR4.5. Thus, it seems that MMR can be achieved upon retreatment after a TFR phase. As in the ENESTfreedom study, the PFS and OS data are immature.

With respect to the data currently available it is of upmost importance to have well defined criteria for the safe and most promising discontinuation of TKI on the one hand, and, on the other, to increase the number of patients available for such an attempt. The MAH has proposed stringent eligibility criteria to be used in discontinuation of the drug, as well as guidance for frequent monitoring of BCR-ABL levels. The criteria are consistent with, some being even more conservative, than the ones used in the previously published TKI treatment discontinuation studies. The criteria are accordingly reflected in the SmPC sections 4.2 and 4.4. The MAH has evaluated previously published studies in CML patients. Among studies evaluating TKI discontinuation (Saussele 2016, Hughes 2016), only one patient progressed to BC. In the ENESTfreedom and ENESTop trials, none of the patients who re-initiated nilotinib therapy progressed to AP/BC. Characterizing patients who are at increased risk of relapse and how to monitor them is crucial. However, the MAH could not identify potential prognostic factors, when multivariate analysis was performed. The risk of developing resistance to the drug (ie. non-responsiveness) when re-treated was evaluated. In the published literature as well as in the study trials, the vast majority of patients who needed re-treatment with TKI did so during the first year after discontinuation, and most commonly during the first 6 months after discontinuation. The patients responded well and achieved MMR in a timely manner. By evaluating the published literature, no patient has developed TKI resistance in TFR that was detected during TKI re-initiation. Further data in the present ENESTfreedom and ENESTop trials did not suggest any resistance mechanisms of the treatment-free interval.

There is continuously growing evidence, which shows that TKI discontinuation could be considered, if the patients are and have been in deep molecular remission for certain period of time, and that patient that relapse, can be safely brought back to remission upon re-initiation of TKI treatment. International guidelines (NCCN guidelines Version 2.2017, CML) provide the option of treatment discontinuation with TKI, if strict criteria are fulfilled. From a clinical point of view a discontinuation or interruption of TKI treatment is considered a benefit to the patients, provided that a treatment free period conveys no increased risk to the patient, the suggested criteria are used, and the patients are being closely monitored by BCR-ABL for a whole life time. Updated data from 96 weeks support the primary findings, however, further data generated over significantly longer periods than currently available are still needed and should be provided post-approval (see Risk Management Plan). Even during long-lasting TFR, persistent CML stem cells are detectable using genomic analyses, but currently the clinical implications of dormant yet detectable leukemic stem cells is unknown and an active area of research. Despite a growing body of evidence supporting the use of genomic PCR methods to detect patient-specific gene fusions, analysis of BCR-ABL at the DNA level has been limited and thus, detecting persistent CML stem cells using these methods do currently not trigger any change in the management of the disease. However, the MAH should collect data on gene signature on patients that relapse on TFR compared to patients that relapse on treatment (see Risk Management Plan).

Discontinuation of treatment may be considered in eligible Philadelphia chromosome positive (Ph+) CML patients in chronic phase who have been treated with nilotinib at 300 mg twice daily for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy (SmPC section 4.2).

The measures proposed below are adequate in view of the remaining uncertainties about long-term

outcomes. A precautionary approach with intensive monitoring until the remaining uncertainties can be addressed is justified (see Risk Management Plan).

Eligible patients who discontinue Tasigna therapy must have their BCR-ABL transcript levels and complete blood count with differential monitored monthly for one year, then every 6 weeks for the second year, and every 12 weeks thereafter. Monitoring of BCR-ABL transcript levels must be performed with a quantitative diagnostic test validated to measure molecular response levels on the International Scale (IS) with a sensitivity of at least MR4.5 (BCR-ABL/ABL ≤0.0032% IS) (SmPC section 4.2).

For patients who lose MR4 (MR4=BCR-ABL/ABL ≤0.01%IS) but not MMR (MMR=BCR-ABL/ABL ≤0.1%IS) during the treatment-free phase, BCR-ABL transcript levels should be monitored every 2 weeks until BCR-ABL levels return to a range between MR4 and MR4.5. Patients who maintain BCR-ABL levels between MMR and MR4 for a minimum of 4 consecutive measurements can return to the original monitoring schedule (SmPC section 4.2).

Patients who lose MMR must re-initiate treatment within 4 weeks of when loss of remission is known to have occurred. Nilotinib therapy should be re-initiated at 300 mg twice daily or at a reduced dose level of 400 mg once daily if the patient had a dose reduction prior to discontinuation of therapy. Patients who re-initiate nilotinib therapy should have their BCR-ABL transcript levels monitored monthly until MMR is re-established and every 12 weeks thereafter (SmPC section 4.2).

Taken together, the present data are clinically relevant and are reflected in sections 4.2, 4.4, 4.6, 4.8 and 5.1 of the SmPC.

Additional expert consultation

Following the CHMP request, a Scientific Advisory Group meeting was convened on 5 April 2017 to provide advice on the following list of questions:

1. Please discuss the potential value of treatment-free remission (TFR) as currently proposed compared to continued treatment in Ph+ CML patients in the present treatment landscape.

In principle, avoiding unnecessary treatment, especially if not well-tolerated, is an important goal in the treatment of CML. Avoidance of toxicity may be an important goal in up to about 30% of patients. However, one needs to balance this goal against the risk of additional anxiety due to a perceived higher risk of loss of remission, as well as the burden of intensive monitoring, which may result for example in frequent visits to the hospital and frequent laboratory examinations. It is also important to promote the option of treatment-free periods to CML patients and relevant healthcare professionals in a balanced way, avoiding the misconception that unless MR4.5 or better is achieved (to allow treatment-free remission) this is perceived by patient as "treatment failure". Thus, adequate information about benefits, risks, uncertainties, follow-up and patient preferences will play a key role in the treatment decision.

From a physician's perspective, while avoiding unnecessary treatment is an important goal, the burden of intensive monitoring also requires careful consideration, taking into account the need to use high quality laboratory testing of molecular response according to agreed international standards, such as the laboratory recommendations, developed as part of the European Treatment and Outcome Study

(EUTOS) for CML, which may not be readily available everywhere in Europe.

2. Please discuss if the precautionary measures provided in the SmPC are adequate with regard to the monitoring of disease activity and the re-initiation of nilotinib.

Currently, the measures proposed are adequate in view of the remaining uncertainties about long-term outcomes (longest follow-up is currently about 12 years for nilotinib; about 16 years for imatinib) as well as the need not to deviate significantly from the measures used in the available studies. A precautionary approach with intensive monitoring until the remaining uncertainties can be addressed is justified. However, efforts to optimise treatment duration and follow-up should continue (see answer to question No. 3).

Strict adherence to the proposed measures should be encouraged since there is a risk that practical considerations may lead to less intense monitoring than is needed and ultimately in delays in detecting loss of remission. The risk management plan should consider if measures are needed to address potential issues with monitoring compliance.

Formally introducing treatment-free periods for nilotinib with changes to the SmPC is likely to have an impact on treatment duration and follow-up of other TKI inhibitors that currently do not allow such an approach as part of the SmPC. In principle, this approach might be applicable to other TKIs and in particular to imatinib. However, there may be small differences between TKIs (for instance shorter time to and greater depth of response may allow shorter treatment duration before stopping) and also differences in the burden of long-term toxicity motivating the treatment-free approach (for instance, the increase in vascular events with nilotinib is continuous with no plateau). Thus, direct extrapolation of the approach among TKIs is not possible. For imatinib and to a lesser extent dasatinib, academic studies addressing TFR are available/ongoing and are likely to influence clinical practice albeit without the rigour of regulatory assessment and agreed risk management measures. Whether this should be addressed at the level of clinical guidelines and/or regulatory assessment (even if based on published data) can be debated (clinical guidelines already include detailed recommendations for follow-up) although a rigorous regulatory assessment is encouraged in view of the evolving level of evidence, remaining uncertainties, and the potential need to introduce adequate risk-minimisation measures.

3. Please discuss whether the data that we already have are sufficient, or whether the CHMP should pursue the generation of additional clinical data to confirm the longer-term outcomes in patients who discontinue treatment when in deep molecular response.

Further data are needed with longer follow-up (beyond 48 months), to confirm the reported plateau without event after 48 months, and to further optimise duration of treatment and follow-up, including further research into dynamics of relapse, factors associated with loss of remission, and development of nilotinib resistance. Studies should be run examining potential differences in patterns of resistance on TKI treatment (including TKI-induced clonal selections) - or off TKI treatment; detailed biological characterizations (e.g., molecular; drug transporter expression and other biological pathways) of the on/off treatment relapses is essential to add value in understanding the potentially different mechanisms in these two scenarios.

2.4.4. Conclusions on the clinical efficacy

Both ENESTfreedom and ENESTop studies provided results indicating that it is possible to discontinue TKI treatment despite the fact that OS and PFS data are immature. Discontinuation of treatment may

be considered in eligible Philadelphia chromosome positive (Ph+) CML patients in chronic phase who have been treated with nilotinib for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy. The precautionary measures included in the SmPC are adequate with regard to the monitoring of disease activity and the re-initiation of nilotinib.

Results from both ENESTfreedom and ENESTop studies do not merit an extension of the indication as initially proposed by the MAH, but are acceptable, to be reflected in sections 4.2, 4.4, 4.6, 4.8 and 5.1 of the SmPC.

2.5. Clinical safety

Introduction

About 10400 patients and healthy volunteers have been exposed in clinical studies. Post-marketing experience is available from more than 39300 patients with CML since approval in 2007.

Additional safety data is based on data from 215 patients in Study I2201 (ENESTfreedom), 163 patients from Study A2408 (ENESTop), and 101 patients from Study A2405 (ENESTcmr) at the recommended 400 mg bid (second-line treatment) or 300 mg bid dosing regimen (first-line treatment) of nilotinib. Of note in Study I2201, patients who did not tolerate the dose of 300 mg bid were treated at 400 mg once daily, and in Study A2408 patients who achieved and sustained MR4.5 on any dose other than 300 mg/400 mg bid of nilotinib prior to study entry, were also included in the study.

This overall safety evaluation is based on data from patients who have been exposed to nilotinib. Study I2201 and Study A2408 enrolled a highly selected population of patients who had tolerated nilotinib for at least two years before entering the consolidation phase for one additional year of exposure. The safety data collected during the consolidation phase may thus be different from the known safety profile of nilotinib in newly diagnosed patients who are initiating treatment with nilotinib. However, this one-year consolidation period is a good reference to compare the patient's safety during the TFR phase with that during the previous nilotinib therapy. Study A2405 (ENESTcmr) enrolled highly selected patients who had demonstrated tolerability to imatinib and had been treated with imatinib for at least two years prior to study entry, whereas the patients randomized to nilotinib were exposed to nilotinib for the first time in the context of the clinical trial. Collectively, the data allows for assessment of the safety profile of nilotinib, provides safety information regarding AEs that may occur upon discontinuation of nilotinib, and assesses the safety of treatment re-initiation in patients requiring such therapy.

Patient exposure

Study I2201 (ENESTfreedom)

Table 29 Exposure of study drug during the NTCS phase and duration of the TFR phase (TFR Safety set) - Study I2201

Exposure variable	NTCS[1] N=190	TFR[2] N=190
Duration of exposure* (weeks)		
Mean (SD)	52.19 (0.841)	35.04 (15.250)
Median	52.14	48.00
25th - 75th percentiles	52.00-52.43	18.00-48.00
Min-Max	50.0-57.6	8.4-48.0
Duration of exposure* category (weeks) - n (%)		
<12	0	12 (6.3)
12 - <24	0	56 (29.5)
24 - <36	0	11 (5.8)
36 - <48	0	11 (5.8)
≥48- <60	190 (100)	100 (52.6)
Average daily dose (mg/day)		
Mean (SD)	588.82 (42.503)	NA
Median	600.00	NA
25th - 75th percentiles	600.00-600.00	NA
Min-Max	400.0-600.0	NA
Actual dose intensity (mg/day)		
Mean (SD)	585.93 (43.740)	NA
Median	600.00	NA
25th - 75th percentiles	599.18-600.00	NA
Min-Max	400.0-600.0	NA
Relative dose intensity (%)		
Mean (SD)	97.65 (7.290)	NA
Median	100.00	NA
25th - 75th percentiles	99.86-100.00	NA
Min-Max	66.7-100.0	NA
Relative dose intensity category (%) -n		
<70	8 (4.2)	NA
70 - <90	8 (4.2)	NA
≥ 90	174 (91.6)	NA

* Duration of exposure for NTCS phase =duration of study treatment in NTCS phase, Duration of exposure for TFR phase = duration of TFR phase (off treatment)

[1]N is the number of patients from the TFR Safety Set.

[2]During first 48 weeks (336 days) in TFR starting from the start day of TFR phase

Average daily dose = Total dose/ Time on treatment, treatment free day(s) are not counted.

Actual dose intensity = Total dose/Duration of exposure, treatment free day(s) are counted.

Relative dose intensity = 100*[(Actual dose intensity)/ (Assigned total daily dose)]. Assigned total daily dose=600 mg/day.

NTCS and TFR phases (TFR Safety set)

As of the data cut-off the median duration of exposure to nilotinib in the NTCS phase was 52.14 weeks, range: 8.6 to 57.6 weeks. 95.3% of the patients were exposed to nilotinib for ≥ 48 weeks. The median duration of exposure to nilotinib in the NTCS phase for patients who entered the TFR phase (TFR Safety set) was also 52.14 weeks (range: 50.0 to 57.6 weeks). As of the data cut-off, the median

duration of the TFR phase (from the start day of the TFR phase to the last day of the TFR phase) was 49.4 weeks (range: 8.4 to 85.0 weeks). The median duration of TFR phase (restricted to the first 48 weeks of the TFR phase) was 48.0 weeks (range: 8.4 to 48.0 weeks).

Most patients in the NTCS phase, and patients in the NTCS phase who entered the TFR phase, received the actual dose that was close to the assigned daily dose. The median actual dose intensity in the NTCS phase was 600 mg/day (25-75th percentile: 599.2 to 600.0 mg/day).

As of the data cut off, the median duration of exposure to nilotinib for patients in the NTRI phase (n=86) was 39.6 weeks (range: 5.0 to 69.7 weeks).

Study A2408 (ENESTop)

Exposure to nilotinib was considered to be appropriate to allow for an adequate assessment of safety. Since the primary interest of this study is to understand the benefit of treatment discontinuation with nilotinib in patients having achieved deep molecular response, particular emphasis is placed on the median duration of the TFR phase, which is considered appropriate to allow assessment of safety upon nilotinib discontinuation.

Table 30 Exposure of study drug during the NTCS phase and duration of the TFR phase (TFR Safety set)- Study A2408

Exposure variable	NTCS[1] N=126	TFR[2] N=126
Duration of exposure* (weeks)		
n	126	126
Mean (SD)	52.2 (1.74)	35.0 (15.87)
Median	52.1	48.0
25th-75th percentile	51.3-53.0	17.0-48.0
Min-Max	46-58	6-48
Duration of exposure* category (weeks)		
n (%)		
<12	0	7 (5.6)
12-<24	0	40 (31.7)
24 - <36	0	5 (4.0)
36 - <48	2 (1.6)	3 (2.4)
≥ 48	124 (98.4)	71 (56.3)
Average daily dose (mg/day)		
n	126	NA
Mean (SD)	669.6 (152.22)	NA
Median	793.3	NA
25th - 75th percentile	599.2 - 800.0	NA
Min - Max	300-800	NA
Actual dose intensity (mg/day)		
n	126	NA
Mean (SD)	665.8 (154.59)	NA
Median	771.8	NA
25th - 75th percentile	596.7-800.0	NA
Min - Max	300-800	NA
Relative dose intensity (%) -n (%)		
<70	20 (15.9)	NA
70 - 90	4 (3.2)	NA
≥ 90	102 (81.0)	NA
Relative dose intensity		
n	126	NA
Mean (SD)	111.0 (25.76)	NA
Median	128.6	NA
25th - 75th percentile	99.5-133.3	NA
Min - Max	50-133	NA

Study A2405 (ENESTcmr)

Up to the cut-off date, the median time on treatment (from first day of treatment to last day of randomized treatment) was 47.2 months in the nilotinib arm; and 37.0 months and 26.7 months in the 400 mg and 600 mg once daily cohorts of the imatinib arm.

Median time on treatment with nilotinib after crossover (from first day of nilotinib treatment after crossover to last day of treatment) for crossover patients (n=46) was 662.5 days (21.8 months).

Up to the cut-off date, the median actual dose intensity was 775.7 mg/day in the nilotinib treatment arm; and 400.0 mg/day and 600 mg/day in the two dose cohorts of the imatinib treatment arm. The median actual dose intensity was 790.4 mg/day for the patients that crossed over to nilotinib.

Adverse events

Study I2201 (ENESTfreedom)

In the safety set, nearly all patients (93.0%) had at least one AE, 18.6% of patients had an SAE, 4.7% of patients had an AE that lead to discontinuation of study drug, and 5 patients died during "all phases" of the study.

Table 31 Overview of adverse events during all phases (Safety set)-Study I2201

	All phases N=215	
Category	**All grades n (%)**	**Grades 3/4 n (%)**
All deaths[1]	5 (2.3)	
On-treatment deaths[2]	5 (2.3)	
Adverse events	200 (93.0)	60 (27.9)
Suspected to be drug-related	110 (51.2)	29 (13.5)
Serious adverse events	40 (18.6)	29 (13.5)
Suspected to be drug-related	13 (6.0)	9 (4.2)
AEs leading to discontinuation	10 (4.7)	8 (3.7)
Suspected to be drug-related	7 (3.3)	5 (2.3)
AEs requiring dose interruption and/or change	23 (10.7)	12 (5.6)
Suspected to be drug-related	12 (5.6)	7 (3.3)
AEs requiring additional therapy	173 (80.5)	43 (20.0)
Suspected to be drug-related	61 (28.4)	18 (8.4)

[1]All deaths including those >30 days after end of last study phase

[2]Deaths occurring >30 days after end of last study phase are not included

Table 32 Overview of adverse events during the NTCS and the TFR phases (TFR Safety set) - Study I2201

	NTCS phase[1] (TFR Safety set): Patients in the NTCS phase who entered the TFR phase N=190		TFR phase[2] (TFR Safety set): Patients who entered the TFR phase from the NTCS phase N=190	
Category	**All grades n (%)**	**Grades 3/4 n (%)**	**All grades n (%)**	**Grades 3/4 n (%)**
On-treatment deaths[3]	0		1 (0.5)	
Adverse events	158 (83.2)	26 (13.7)	125 (65.8)	21 (11.1)
Serious adverse events	13 (6.8)	9 (4.7)	12 (6.3)	10 (5.3)
AEs leading to discontinuation	0	0	0	0
AEs requiring dose interruption and/or change	10 (5.3)	4 (2.1)	0	0
AEs requiring additional therapy	119 (62.6)	21 (11.1)	94 (49.5)	15 (7.9)

[1]N is the number of patients from the TFR Safety Set.

[2]During first 48 weeks (336 days) in TFR starting from the start day of TFR phase.

[3]Deaths occurring >30 days after end of last study phase are not included TFR=treatment-free remission; NTCS= Nilotinib treatment consolidation

Most frequently occurring adverse events in Study I2201 (ENESTfreedom)

Adverse events (all grades) were reported in 83.2% of patients in the NTCS phase (TFR Safety set) as compared to 65.8% of patients in the TFR phase (TFR Safety set). These were

primarily grade 1/2 AEs. The AEs that were reported at a higher incidence by preferred term (≥ 3% difference) in the NTCS phase (TFR Safety set) compared to the TFR phase were: hypophosphatemia (+6.8% difference), hypertension (+4.2% difference), cough (+3.7% difference), rash (+3.7% difference), and bronchitis (+3.2% difference). The most frequent grade 3/4 AEs reported in the NTCS phase (TFR Safety set) were: hypertension (5.3%), hypophosphatemia (1.6%), and lipase increased (1.1%). The AEs that were reported at a higher incidence by preferred term (≥ 3% difference) in the TFR phase compared to the NTCS phase (TFR Safety set) were: arthralgia (+3.7% difference), pain in extremity (+3.7% difference), and myalgia (+3.6% difference). The most frequent grade 3/4 AEs reported in the TFR phase were: hypertension, arthralgia, lipase increased, dyspnea, and peripheral arterial occlusive (1.1% each).

Table 33 Adverse events regardless of study drug relationship by preferred term and maximum grade (greater than 2% in either phase) during the NTCS and the TFR phases (TFR Safety set) Study I2201

	NTCS[1] phase N=190		TFR[2] phase N=190	
Preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Total	**158 (83.2)**	**26 (13.7)**	**125 (65.8)**	**21 (11.1)**
Nasopharyngitis	21 (11.1)	0	16 (8.4)	0
Arthralgia	16 (8.4)	0	23 (12.1)	2 (1.1)
Hypertension	15 (7.9)	10 (5.3)	7 (3.7)	2 (1.1)
Hypophosphataemia	15 (7.9)	3 (1.6)	2 (1.1)	0
Diarrhoea	11 (5.8)	0	8 (4.2)	1 (0.5)
Headache	10 (5.3)	0	10 (5.3)	0
Abdominal Pain Upper	9 (4.7)	0	7 (3.7)	1 (0.5)
Back Pain	9 (4.7)	1 (0.5)	6 (3.2)	0
Fatigue	8 (4.2)	0	6 (3.2)	0
Bronchitis	7 (3.7)	0	1 (0.5)	0
Cough	7 (3.7)	0	0	0
Influenza	7 (3.7)	0	4 (2.1)	0
Lipase Increased	7 (3.7)	2 (1.1)	2 (1.1)	2 (1.1)
Nausea	7 (3.7)	0	3 (1.6)	1 (0.5)
Pyrexia	7 (3.7)	0	2 (1.1)	0
Rash	7 (3.7)	0	0	0
Dizziness	6 (3.2)	1 (0.5)	1 (0.5)	0
Muscle Spasms	6 (3.2)	0	3 (1.6)	0
Musculoskeletal Pain	6 (3.2)	1 (0.5)	5 (2.6)	0
Upper Respiratory Tract Infection	6 (3.2)	0	8 (4.2)	0
Alopecia	5 (2.6)	0	1 (0.5)	0
Asthenia	5 (2.6)	0	1 (0.5)	0
Blood Cholesterol Increased	5 (2.6)	0	4 (2.1)	0
Dry Skin	5 (2.6)	0	1 (0.5)	0
Dyspnoea	5 (2.6)	0	2 (1.1)	2 (1.1)
Fall	5 (2.6)	0	0	0
Herpes Zoster	5 (2.6)	1 (0.5)	1 (0.5)	0
Pain In Extremity	5 (2.6)	0	12 (6.3)	0
Vomiting	5 (2.6)	0	5 (2.6)	0
Abdominal Pain	4 (2.1)	1 (0.5)	4 (2.1)	0
Blood Bilirubin Increased	4 (2.1)	1 (0.5)	0	0
Bone Pain	4 (2.1)	0	8 (4.2)	1 (0.5)
Contusion	4 (2.1)	0	0	0
Folliculitis	4 (2.1)	0	0	0
Oropharyngeal Pain	4 (2.1)	0	0	0
Pruritus	4 (2.1)	0	1 (0.5)	0
Myalgia	2 (1.1)	0	9 (4.7)	0
Urinary Tract Infection	2 (1.1)	0	4 (2.1)	0

Tendonitis	1 (0.5)	0	4 (2.1)	0

Preferred terms are sorted in descending frequency of All grades column, as reported in the Consolidation (NTCS) column.
A patient with multiple occurrences of an AE under one phase is counted only once in the AE category for that phase.
A patient with multiple adverse events is counted only once in the total row.
[1]N is the number of patients from the TFR Safety Set.
[2]During first 48 weeks (336 days) in TFR starting from the start day of TFR phase.

Study A2408 (ENESTop)

Eighty-nine percent of patients had at least one AE, 20.9% of patients had an SAE, 6.1% of patients had an AE that led to discontinuation of study drug, and one patient died during the consolidation phase of the study.

Table 34 Overview of adverse events during all phases (Safety set)-Study A2408

	All phases N=163	
Category	**All grades n (%)**	**Grades 3/4 n (%)**
All deaths[1]	1 (0.6)	
On-treatment deaths[2]	1 (0.6)	
Adverse events	145 (89.0)	50 (30.7)
Suspected to be drug-related	75 (46.0)	18 (11.0)
Serious adverse events	34 (20.9)	30 (18.4)
Suspected to be drug-related	10 (6.1)	8 (4.9)
AEs leading to discontinuation	10 (6.1)	8 (4.9)
Suspected to be drug-related	7 (4.3)	5 (3.1)
AEs requiring dose interruption and/or change	36 (22.1)	18 (11.0)
Suspected to be drug-related	18 (11.0)	10 (6.1)
AEs requiring additional therapy	130 (79.8)	40 (24.5)
Suspected to be drug-related	50 (30.7)	11 (6.7)

[1]All deaths including those >30 days after end of last study phase
[2]Deaths occurring >30 days after end of last study phase are not included

Table 35 Overview of adverse events during the NTCS and the TFR phases (TFR Safety set) - Study A2408

	NTCS phase[1] (TFR Safety set): Patients in the NTCS phase who entered the TFR phase		**TFR phase[2] (TFR Safety set): Patients who entered the TFR phase from the NTCS phase**	
Category	**All grades n (%)**	**Grades ¾ n (%)**	**All grades n (%)**	**Grades 3/4 n (%)**
On-treatment deaths[3]	0	-	0	-
Adverse events	97 (77.0)	26 (20.6)	93 (73.8)	17 (13.5)
Serious adverse events	15 (11.9)	14 (11.1)	6 (4.8)	6 (4.8)
AEs leading to discontinuation	0	0	0	0
AEs requiring dose interruption and/or change	21 (16.7)	11 (8.7)	0	0
AEs requiring additional therapy	76 (60.3)	20 (15.9)	75 (59.5)	13 (10.3)

[1]N is the number of patients from the TFR Safety set.

[2]During first 48 weeks (336 days) in TFR starting from the start day of TFR phase.
[3]Deaths occurring >30 days after end of last study phase are not included.

Most frequently occurring adverse events in Study A2408 (ENESTop) in the NTCS and TFR phases in trial A2408 (ENESTop):

For the 126 patients who entered the TFR phase, the incidence of AEs was comparable in the NTCS and the TFR phases (77% and 73.8%, respectively). The preferred terms that were reported at a higher incidence (≥ 3% difference) in the NTCS phase (TFR Safety set) compared to the TFR phase were: constipation and rash (+4.8% difference each); and eczema and gastroenteritis (+3.2% difference each). Grade 3/4 AEs reported in at least two patients in the NTCS phase were: hypertension (3.2%), lipase increased (2.4%), pneumonia (1.6%), atrial fibrillation (1.6%), and hepatotoxicity (1.6%). The preferred terms that were reported at a higher incidence (≥ 3% difference) in the TFR phase compared to the NTCS phase (TFR Safety set) were: arthralgia (+16.7% difference), myalgia (+9.5% difference), musculoskeletal pain (+5.5% difference), increased weight (+4.8% difference), cough (+4% difference), and oral herpes (+3.2% difference). Grade 3/4 AEs reported in at least two patients in the TFR phase were: hypertension (1.6%); cellulitis (1.6%), and carpel tunnel syndrome (1.6%).

Table 36 Adverse events regardless of study drug relationship by preferred term and maximum grade (greater than 2% in either phase) during the NTCS and the TFR phases (TFR Safety set) Study A2408

	NTCS phase[1] N=126		TFR phase[2] N=126	
	All grades	Grade ¾	All grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)
Total	97 (77.0)	26 (20.6)	93 (73.8)	17 (13.5)
Hypertension	9 (7.1)	4 (3.2)	7 (5.6)	2 (1.6)
Arthralgia	8 (6.3)	0	29 (23.0)	1 (0.8)
Nasopharyngitis	8 (6.3)	0	5 (4.0)	0
Pain in extremity	7 (5.6)	0	9 (7.1)	0
Constipation	6 (4.8)	1 (0.8)	0	0
Headache	6 (4.8)	0	4 (3.2)	0
Rash	6 (4.8)	0	0	0
Fatigue	5 (4.0)	1 (0.8)	3 (2.4)	0
Abdominal pain	4 (3.2)	0	2 (1.6)	0
Alopecia	4 (3.2)	0	1 (0.8)	0
Diarrhoea	4 (3.2)	1 (0.8)	5 (4.0)	0
Dyspepsia	4 (3.2)	0	2 (1.6)	0
Eczema	4 (3.2)	0	0	0
Gastroenteritis	4 (3.2)	1 (0.8)	0	0
Muscle spasms	4 (3.2)	0	1 (0.8)	0
Myalgia	4 (3.2)	0	16 (12.7)	0
Nausea	4 (3.2)	0	2 (1.6)	0
Upper respiratory tract infection	4 (3.2)	0	2 (1.6)	0
Urinary tract infection	4 (3.2)	0	4 (3.2)	0
Vomiting	4 (3.2)	0	1 (0.8)	0
Abdominal pain upper	3 (2.4)	0	1 (0.8)	0
Back pain	3 (2.4)	1 (0.8)	0	0
Dry skin	3 (2.4)	0	0	0
Dyspnoea	3 (2.4)	0	0	0
Gout	3 (2.4)	0	1 (0.8)	1 (0.8)
Hypercholesterolaemia	3 (2.4)	0	0	0
Lipase increased	3 (2.4)	3 (2.4)	1 (0.8)	1 (0.8)
Muscle contracture	3 (2.4)	0	1 (0.8)	0
Pneumonia	3 (2.4)	2 (1.6)	2 (1.6)	1 (0.8)
Pyrexia	3 (2.4)	0	1 (0.8)	0
Sinusitis	3 (2.4)	0	2 (1.6)	0
Weight decreased	3 (2.4)	0	0	0
Alanine aminotransferase increased	2 (1.6)	0	3 (2.4)	1 (0.8)
Bone pain	2 (1.6)	0	4 (3.2)	0
Influenza	2 (1.6)	1 (0.8)	4 (3.2)	0
Insomnia	2 (1.6)	0	3 (2.4)	0
Musculoskeletal pain	2 (1.6)	0	9 (7.1)	0
Oedema peripheral	2 (1.6)	0	3 (2.4)	0
Cough	1 (0.8)	0	6 (4.8)	0
Osteoarthritis	1 (0.8)	0	3 (2.4)	0
Pain	1 (0.8)	0	3 (2.4)	1 (0.8)
Oral herpes	0	0	4 (3.2)	0
Pharyngitis	0	0	3 (2.4)	0
Weight increased	0	0	6 (4.8)	0

NTCS=nilotinib treatment consolidation; TFR=treatment-free remission
Preferred terms are sorted in descending frequency of All grades column, as reported in the NTCS column
A patient with multiple occurrences of an AE under one phase is counted only once in the AE category for that phase.
A patient with multiple adverse events is counted only once in the total row.
[1] N is the number of patients from the TFR Safety set.
[2] During first 48 weeks (336 days) in TFR starting from the start day of TFR phase.

Study A2405 (ENESTcmr)

Table 37 Overview of adverse events (Safety set) - Study A2405

	Nilotinib		**Imatinib**	
	N=101		**N=103**	
	All grades	**Grade 3/4**	**All grades**	**Grade 3/4**
Category	**n (%)**	**n (%)**	**n (%)**	**n (%)**
All deaths[1]	3 (3.0)	3 (3.0)	3 (2.9)	3 (2.9)
On-treatment deaths[2]	2 (2.0)	2 (2.0)	1 (1.0)	1 (1.0)
Adverse events	101 (100.0)	51 (50.5)	98 (95.1)	28 (27.2)
Suspected to be drug-related	94 (93.1)	41 (40.6)	73 (70.9)	9 (8.7)
Serious adverse events	21 (20.8)	15 (14.9)	16 (15.5)	14 (13.6)
Suspected to be drug-related	9 (8.9)	6 (5.9)	1 (1.0)	0
AEs leading to discontinuation	21 (20.8)	11 (10.9)	7 (6.8)	5 (4.9)
Suspected to be drug-related	20 (19.8)	11 (10.9)	3 (2.9)	1 (1.0)
AEs requiring dose interruption and/or change	59 (58.4)	32 (31.7)	19 (18.4)	8 (7.8)
Suspected to be drug-related	52 (51.5)	29 (28.7)	8 (7.8)	4 (3.9)
AEs requiring additional therapy	14 (13.9)	5 (5.0)	18 (17.5)	7 (6.8)
Suspected to be drug-related	2 (2.0)	2 (2.0)	3 (2.9)	0

[1]All deaths including those >28 days after end of treatment
[2]All deaths on treatment and within 28 days after end of treatment

Table 38 Overview of adverse events in patients who crossed over to nilotinib (Safety set) – Study A2405

Category	**All grades n (%)**	**Grade 3/4 n (%)**
All deaths[1]	0	
On-treatment deaths[2]	0	
Adverse events	43 (93.5)	20 (43.5)
Suspected to be drug-related	37 (80.4)	16 (34.8)
Serious adverse events	8 (17.4)	5 (10.9)
Suspected to be drug-related	5 (10.9)	2 (4.3)
AEs leading to discontinuation	6 (13.0)	4 (8.7)
Suspected to be drug-related	6 (13.0)	4 (8.7)
AEs requiring dose interruption and/or change	20 (43.5)	10 (21.7)
Suspected to be drug-related	15 (32.6)	7 (15.2)
AEs requiring additional therapy	4 (8.7)	2 (4.3)
Suspected to be drug-related	1 (2.2)	1 (2.2)

1All deaths including those >28 days after end of treatment

2All deaths on treatment and within 28 days after end of treatment

Table 39 Adverse events irrespective of causality by preferred term and maximum grade (occurring in at least 5% in either groups) (Safety set) - Study A2405

	All grades		CTC grade 3 or 4	
Preferred term	Nilotinib N=101 n (%)	Imatinib N=103 n (%)	Nilotinib N=101 n (%)	Imatinib N=103 n (%)
Total	101 (100.0)	98 (95.1)	51 (50.5)	28 (27.2)
Headache	43 (42.6)	13 (12.6)	2 (2.0)	0
Nausea	22 (21.8)	16 (15.5)	0	0
Rash	30 (29.7)	4 (3.9)	1 (1.0)	0

	All grades		CTC grade 3 or 4	
Preferred term	Nilotinib N=101 n (%)	Imatinib N=103 n (%)	Nilotinib N=101 n (%)	Imatinib N=103 n (%)
Upper respiratory tract infection	20 (19.8)	14 (13.6)	0	0
Diarrhoea	14 (13.9)	19 (18.4)	1 (1.0)	1 (1.0)
Muscle spasms	15 (14.9)	18 (17.5)	0	0
Lipase increased	19 (18.8)	13 (12.6)	12 (11.9)	1 (1.0)
Pruritus	30 (29.7)	0	1 (1.0)	0
Arthralgia	16 (15.8)	10 (9.7)	1 (1.0)	0
Alanine aminotransferase increased	19 (18.8)	5 (4.9)	2 (2.0)	1 (1.0)
Aspartate aminotransferase increased	14 (13.9)	10 (9.7)	0	1 (1.0)
Fatigue	16 (15.8)	8 (7.8)	1 (1.0)	1 (1.0)
Hypophosphataemia	9 (8.9)	13 (12.6)	3 (3.0)	5 (4.9)
Back pain	12 (11.9)	9 (8.7)	0	0
Abdominal pain	12 (11.9)	8 (7.8)	1 (1.0)	0
Abdominal pain upper	13 (12.9)	7 (6.8)	0	0
Cough	11 (10.9)	9 (8.7)	0	0
Dry skin	20 (19.8)	0	0	0
Anaemia	6 (5.9)	12 (11.7)	1 (1.0)	1 (1.0)
Influenza	9 (8.9)	9 (8.7)	0	0
Musculoskeletal pain	10 (9.9)	8 (7.8)	0	0
Pain in extremity	14 (13.9)	4 (3.9)	0	0
Hypercholesterolaemia	11 (10.9)	6 (5.8)	0	0
Insomnia	12 (11.9)	5 (4.9)	0	0
Vomiting	11 (10.9)	6 (5.8)	1 (1.0)	0
Amylase increased	9 (8.9)	7 (6.8)	0	0
Blood creatinine increased	6 (5.9)	10 (9.7)	0	0
Hypertension	10 (9.9)	6 (5.8)	1 (1.0)	1 (1.0)
Myalgia	14 (13.9)	2 (1.9)	1 (1.0)	0
Constipation	15 (14.9)	0	1 (1.0)	0
Weight decreased	10 (9.9)	5 (4.9)	0	0
Decreased appetite	8 (7.9)	6 (5.8)	0	0
Nasopharyngitis	9 (8.9)	5 (4.9)	0	0
Asthenia	9 (8.9)	4 (3.9)	0	0
Oedema peripheral	6 (5.9)	7 (6.8)	0	0
Globulins decreased	4 (4.0)	8 (7.8)	0	0
Oropharyngeal pain	6 (5.9)	6 (5.8)	0	0
Alopecia	11 (10.9)	0	0	0
Blood bilirubin increased	10 (9.9)	1 (1.0)	2 (2.0)	1 (1.0)
Dizziness	5 (5.0)	6 (5.8)	0	0
Influenza like illness	8 (7.9)	3 (2.9)	0	0
Blood cholesterol increased	8 (7.9)	2 (1.9)	0	0
Blood creatine phosphokinase increased	1 (1.0)	9 (8.7)	0	0
Depression	6 (5.9)	4 (3.9)	0	0
Gamma-glutamyltransferase increased	8 (7.9)	2 (1.9)	1 (1.0)	1 (1.0)
Hyperbilirubinaemia	10 (9.9)	0	0	0
Hyperglycaemia	4 (4.0)	6 (5.8)	0	0
Hypertriglyceridaemia	3 (3.0)	7 (6.8)	0	0
Pain	7 (6.9)	3 (2.9)	0	0
Pyrexia	5 (5.0)	4 (3.9)	0	0
Urinary tract infection	8 (7.9)	1 (1.0)	0	0

	All grades		CTC grade 3 or 4	
Preferred term	Nilotinib N=101 n (%)	Imatinib N=103 n (%)	Nilotinib N=101 n (%)	Imatinib N=103 n (%)
Dyslipidaemia	5 (5.0)	3 (2.9)	0	0
Folliculitis	8 (7.9)	0	0	0
High density lipoprotein decreased	2 (2.0)	6 (5.8)	0	1 (1.0)
Tonsillitis	5 (5.0)	3 (2.9)	0	0
Conjunctival haemorrhage	1 (1.0)	6 (5.8)	0	0
Hyperuricaemia	5 (5.0)	2 (1.9)	0	0
Paraesthesia	5 (5.0)	2 (1.9)	0	0

The AEs reported that were reported at a higher incidence by preferred term in the nilotinib group compared to the imatinib group (≥ 10% difference) were: headache (+30% difference), rash (+25.8% difference), pruritus (+29.7% difference), dry skin (+19.8% difference), constipation (14.9% difference), elevated ALT (+13.9% difference), myalgia (+12% difference), alopecia (10.9% difference), and pain in extremity (10% difference). The most common grade 3/4 event reported in association with nilotinib was lipase increased (in 11.9% of patients) (Table 5-9).

In the group of patients who had crossed-over to nilotinib, the most frequently occurring AE was rash in 9 patients (19.6%) followed by ALT increased, headache and pain in extremity in 8 patients (17.4%) each. The AE headache in two patients was of grade 3/4 severity.

Serious adverse event/deaths/other significant events

Serious adverse event

Study I2201 (ENESTfreedom)

Table 40 Serious adverse events, regardless of study drug relationship by preferred term in the NTCS and the TFR phases (TFR Safety set) Study I2201

Preferred term	NTCS[1] N=190 n (%)	TFR[2] N=190 n (%)
Total	**13 (6.8)**	**12 (6.3)**
Inguinal Hernia	2 (1.1)	0
Intervertebral Disc Protrusion	2 (1.1)	1 (0.5)
Pancreatitis	2 (1.1)	0
Abdominal Pain	1 (0.5)	0
Basal Cell Carcinoma	1 (0.5)	0
Contrast Media Allergy	1 (0.5)	0
Dacryocystitis	1 (0.5)	0
Dizziness	1 (0.5)	0
Drug Hypersensitivity	1 (0.5)	0
Gastric Ulcer	1 (0.5)	0
Headache	1 (0.5)	0
Iris Neovascularisation	1 (0.5)	0
Malignant Melanoma	1 (0.5)	0
Multiple Sclerosis Relapse	1 (0.5)	0
Myocardial Infarction	1 (0.5)	0
Peripheral Arterial Occlusive Disease	1 (0.5)	2 (1.1)
Pharyngeal Abscess	1 (0.5)	0
Sciatica	1 (0.5)	0
Thyroid Neoplasm	1 (0.5)	0

Urinary Incontinence	1 (0.5)	0
Abdominal Pain Upper	0	1 (0.5)
Ankle Fracture	0	1 (0.5)
Ascites	0	1 (0.5)
Cardiac Failure Congestive	0	1 (0.5)
Cerebral Infarction	0	1 (0.5)
Cholelithiasis	0	1 (0.5)
Death	0	1 (0.5)
Dyspnoea	0	1 (0.5)
Haemorrhoids	0	1 (0.5)
Mesothelioma	0	1 (0.5)
Nausea	0	1 (0.5)
Pleural Effusion	0	1 (0.5)
Rectal Cancer	0	1 (0.5)
Rotator Cuff Syndrome	0	1 (0.5)
Type 2 Diabetes Mellitus	0	1 (0.5)

Preferred terms are sorted in descending frequency of All grades column, as reported in the Consolidation (NTCS) column.

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.

[1]N is the number of patients from the TFR Safety Set.

[2]During first 48 weeks (336 days) in TFR starting from the start day of TFR phase.

Study A2408 (ENESTop)

Table 41 Serious adverse events regardless of study drug relationship by preferred term in the consolidation and TFR phases (TFR Safety set) Study A2408

Preferred term	NTCS[1] N=126 All grades n (%)	TFR[2] N=126 All grades n (%)
Total	**15 (11.9)**	**6 (4.8)**
Atrial fibrillation	2 (1.6)	0
Pneumonia	2 (1.6)	1 (0.8)
Acute myocardial infarction	1 (0.8)	0
Asthma	1 (0.8)	0
Atrioventricular block	1 (0.8)	0
Back Pain	1 (0.8)	0
Cellulitis	1 (0.8)	2 (1.6)
Constipation	1 (0.8)	0
Coronary artery disease	1 (0.8)	0
Diarrhoea	1 (0.8)	0
Diverticulitis	1 (0.8)	0
Gastroenteritis	1 (0.8)	0
Influenza	1 (0.8)	0
Ligament sprain	1 (0.8)	0
Metrorrhagia	1 (0.8)	0
Muscle spasms	1 (0.8)	0
Peripheral arterial occlusive disease	1 (0.8)	0
Renal failure	1 (0.8)	0
Sinus tachycardia	1 (0.8)	0
Cardiac failure congestive	0	1 (0.8)
Carpal tunnel syndrome	0	1 (0.8)
Haematology test abnormal	0	1 (0.8)
Type 2 diabetes mellitus	0	1 (0.8)

NTCS=nilotinib treatment consolidation; TFR=treatment-free remission
Preferred terms are sorted in descending frequency of All grades column, as reported in the NTCS column
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.
[1] N is the number of patients from the TFR Safety set.
[2] During first 48 weeks (336 days) in TFR starting from the start day of TFR phase.

Study A2405 (ENESTcmr)

Serious adverse events were reported more frequently for patients receiving treatment with nilotinib (21 patients, 20.8% vs. 16 patients, 15.5% for the imatinib group). The incidence of specific SAEs was low for both treatment groups and all events reported were single cases with the exception of atrial fibrillation, prostate cancer, cellulitis, nephrolithiasis and pleural effusion, where two patients from the imatinib treatment group reported this event.

Deaths

Study I2201 (ENESTfreedom)

A total of five patients died during the study by the data cut-off date; two (0.9%) patients died during the NTCS phase, one (0.5%) patient died during the TFR phase, and two (2.3%) patients died during the NTRI phase. The reasons for deaths were cardiac arrest (one patient) and completed suicide (one patient) during the NTCS phase, death-unknown reason (one patient) during the TFR phase, and acute myocardial infarction (one patient), and death-unknown reason (one patient) during the NTRI phase.

Table 42 On treatment deaths by preferred term and by study phase (safety set)- study I2201

Primary cause of death Preferred term	NTCS N=215 n (%)	TFR N=190 n (%)	NTRI N=86 n (%)	NTCT N=13 n (%)	TFR-2 N=8 n (%)	NTRI-2 N=0 n (%)	NTCT-P N=2 n (%)	All N=215 n (%)
Total	2 (0.9)	1 (0.5)	2 (2.3)	0	0	0	0	5 (2.3)
Other*	2 (0.9)	1 (0.5)	2 (2.3)	0	0	0	0	5 (2.3)
Acute myocardial infarction	0	0	1 (1.2)	0	0	0	0	1 (0.5)
Cardiac arrest	1 (0.5)	0	0	0	0	0	0	1 (0.5)
Completed suicide	1 (0.5)	0	0	0	0	0	0	1 (0.5)
Death**	0	1 (0.5)	1 (1.2)	0	0	0	0	2 (0.9)

Preferred terms are sorted in descending frequency as reported overall.
Deaths occurring >30 days after end of last study phase are not included.
*Other than study indication
** Death cause unknown
NTCS=nilotinib treatment consolidation; TFR=treatment-free remission;
NTCT=nilotinib treatment continuation; NTRI=nilotinib treatment re-initiation;
NTCT-P=nilotinib treatment prolonged continuation.

Study A2408 (ENESTop)

One patient (0.6%) died during the course of the study. This death occurred on treatment during the NTCS phase of the study and the cause of death was arterial hemorrhage.

Study A2405 (ENESTcmr)

Of the 204 patients in the Safety Set, as of the 24-month cut-off date, one patient in the nilotinib group died due to an event of acute myocardial infarction within 28 days following study drug discontinuation. The event was of grade 4 severity and suspected to be related to study drug by the Investigator.

Up to the 48-month cut-off date, two additional on treatment deaths have been observed (one in the nilotinib group due to cardiopulmonary failure and one in the imatinib group due to metastases to the peritoneum. Three patients died more than 28 days after study drug discontinuation (one in the nilotinib group due to liver failure from light chain deposition and two in the imatinib group due to metastatic non-small cell lung cancer, prostate cancer with bone metastasis).

Other significant events

Study I2201 (ENESTfreedom)

Table 43 AESI groupings by maximum grade in the NTCS and TFR phases (TFR Safety set)

AESI group	NTCS[1] N=190		TFR[2] N=190	
	All grades n (%)	Grades 3/4 n (%)	All grades n (%)	Grades 3/4 n (%)
Total	**56 (29.5)**	**5 (2.6)**	**61 (32.1)**	**6 (3.2)**
All CVEs	4 (2.1)	2 (1.1)	5 (2.6)	3 (1.6)
Ischemic cerebrovascular events (ICD)	1 (0.5)	0	2 (1.1)	1 (0.5)
Ischemic Heart Disease (IHD)	2 (1.1)	1 (0.5)	0	0
Peripheral Arterial Occlusive Disease (PAOD)	1 (0.5)	1 (0.5)	2 (1.1)	2 (1.1)
Others	0	0	1 (0.5)	0
Blood cholesterol increased	7 (3.7)	0	6 (3.2)	0
Blood glucose increased	3 (1.6)	0	1 (0.5)	0
Cardiac failure	0	0	1 (0.5)	1 (0.5)
Fluid retention	4 (2.1)	0	8 (4.2)	1 (0.5)
Edema and Other Fluid Retentions	3 (1.6)	0	7 (3.7)	1 (0.5)
Severe	1 (0.5)	0	1 (0.5)	0
Hepatotoxicity (Drug induced Liver injury)	0	0	1 (0.5)	1 (0.5)
Musculoskeletal Pain	31 (16.3)	1 (0.5)	47 (24.7)	2 (1.1)
Myelosuppression(Thrombocytopenia)	2 (1.1)	0	0	0
Pancreatitis	3 (1.6)	2 (1.1)	0	0
QT prolongation	2 (1.1)	0	1 (0.5)	0
Rash	8 (4.2)	0	2 (1.1)	0
Significant Bleeding[3]	2 (1.1)	0	0	0
GI hemorrhage	2 (1.1)	0	0	0

AESI groupings consist of one or more adverse events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment.

[1] N is the number of patients from the TFR Safety Set.

[2] During the first 48 weeks in TFR starting from the start day of the TFR phase.

[3] The AESI category "Significant bleeding" includes only events pertaining to the two subcategories that have been considered of interest for Tasigna evaluation, namely CNS hemorrhage and GI hemorrhage. Other types of hemorrhage are not included in this category.

Study A2408(ENESTop)

Table 44 AESI groupings by maximum grade in the consolidation and TFR phases (TFR Safety Set) Study A2408

Adverse events of special interest groups	NTCS[1] N=126		TFR[2] N=126	
	All grades n(%)	Grade 3/4 n(%)	All grades n(%)	Grade 3/4 n(%)
Total	**35 (27.8)**	**6 (4.8)**	**61 (48.4)**	**4 (3.2)**
Cardiovascular disease	6 (4.8)	3 (2.4)	0	0
Ischemic heart disease (IHD)	2 (1.6)	2 (1.6)	0	0
Peripheral arterial occlusive disease (PAOD)	4 (3.2)	1 (0.8)	0	0
Ischemic cerebrovascular disease (ICD)	0	0	0	0
Other	0	0	0	0
Blood cholesterol increased	3 (2.4)	0	1 (0.8)	0
Blood glucose increased	1 (0.8)	0	1 (0.8)	0
Cardiac failure	0	0	1 (0.8)	1 (0.8)
Fluid retention	2 (1.6)	0	13 (10.3)	0
Oedema and other fluid retentions	2 (1.6)	0	13 (10.3)	0
Hepatotoxicity (drug induced liver injury)	2 (1.6)	2 (1.6)	1 (0.8)	1 (0.8)
Musculoskeletal pain	18 (14.3)	0	53 (42.1)	2 (1.6)
QT prolongation	1 (0.8)	0	0	0

Rash	6 (4.8)	0	0	0
Renal events	1 (0.8)	1 (0.8)	0	0
Significant bleeding[3]	0	0	1 (0.8)	0
GI hemorrhage	0	0	1 (0.8)	0

NTCS=nilotinib treatment consolidation; TFR=treatment-free remission

[1]N is the number of patients from the TFR Safety set.

[2]During first 48 weeks (336 days) in TFR starting from the start day of the TFR phase.

[3]The AESI category "Significant bleeding" includes only events pertaining to the two subcategories that have been considered of interest for Tasigna evaluation, namely CNS hemorrhage and GI hemorrhage. Other types of hemorrhage are not included in this category.

Study A2405 (ENESTcmr)

AESI up to crossover which were reported at a higher incidence (≥ 5% difference) in the nilotinib group compared to the imatinib group included: all cardiovascular events (12.9% vs. 1.9%), blood cholesterol increased (16.8% vs. 7.8%), and rashes (40.6% vs. 6.8%).

Laboratory findings

Study I2201 (ENESTfreedom)

Table 45 Worst post-baseline hematology value based on CTC grade during the NTCS and TFR phases (TFR Safety set) Study I2201

	Consolidation (NTCS)[1] N=190			TFR[2] N=190		
	Grade 1/2	Grade 3	Grade 4	Grade 1/2	Grade 3	Grade 4
Parameter	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hemoglobin (g/L) (Hypo)	46 (24.2)	0	0	37 (19.5)	1 (0.5)	0
Leukocytes (10E9/L) (Hypo)	11 (5.8)	0	0	16 (8.4)	0	0
Lymphocytes (absolute) (10^9/L) (Hyper)	7 (3.7)	0	0	8 (4.2)	0	0
Lymphocytes (absolute) (10^9/L) (Hypo)	16 (8.4)	1 (0.5)	0	26 (13.7)	0	0
Neutrophils (absolute) (10^9/L) (Hypo)	5 (2.6)	0	0	10 (5.3)	1 (0.5)	0
Platelets (10^9/L) (Hypo)	16 (8.4)	0	0	20 (10.5)	0	0

Patients are counted only for the worst grade observed post-baseline in the corresponding phase.
% Is based on N.
[1]N is the number of patients from the TFR Safety Set.
[2]During first 48 weeks in TFR starting from the start day of TFR phase.

Table 46 Worst post-baseline biochemistry value based on CTC grade during the NTCS and TFR phases (TFR Safety set) Study I2201

	NTCS[1] N=190			TFR[2] N=190		
	Grade 1/2	Grade 3	Grade 4	Grade 1/2	Grade 3	Grade 4
Parameter	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Alanine aminotransferase (U/L) (Hyper)	71 (37.4)	0	0	24 (12.6)	0	0
Alkaline phosphatase (U/L) (Hyper)	8 (4.2)	0	0	11 (5.8)	0	0
Aspartate aminotransferase (U/L) (Hyper)	30 (15.8)	0	0	13 (6.8)	0	0
Bilirubin (umol/L) (Hyper)	54 (28.4)	3 (1.6)	0	6 (3.2)	0	0
Calcium Corrected (mmol/L) (Hyper)	0	0	0	2 (1.1)	0	0

Calcium Corrected (mmol/L) (Hypo)	17 (8.9)	0	0	1 (0.5)	0	0
Creatinine (umol/L) (Hyper)	27 (14.2)	0	0	23 (12.1)	0	0
Glucose, serum, fasting (mmol/L) (Hyper)	74 (38.9)	1 (0.5)	0	36 (18.9)	1 (0.5)	0
Glucose, serum, fasting (mmol/L) (Hypo)	25 (13.2)	0	0	28 (14.7)	0	0
Magnesium (mmol/L) (Hyper)	2 (1.1)	0	0	0	0	0
Magnesium (mmol/L) (Hypo)	1 (0.5)	0	0	1 (0.5)	0	0
Phosphate (mmol/L) (Hypo)	83 (43.7)	6 (3.2)	0	14 (7.4)	0	0
Potassium (mmol/L) (Hyper)	8 (4.2)	0	0	7 (3.7)	1 (0.5)	0
Potassium (mmol/L) (Hypo)	3 (1.6)	0	0	1 (0.5)	0	0
Triacylglycerol lipase (U/L) (Hyper)	51 (26.8)	5 (2.6)	1 (0.5)	19 (10.0)	3 (1.6)	0

Patients are counted only for the worst grade observed post-baseline.

% is based on N.

The cholesterol and triglyceride collection was added in protocol amendment 2 at the time when most patients had already completed NTCS phase. Thus, cholesterol and triglyceride values are not presented in this table to compare NTCS phase and TFR phase.

[1]N is the number of patients from the TFR Safety Set.

[2]During first 48 weeks in TFR starting from the start day of TFR phase.

Study A2408 (ENESTop)

Table 47 Worst post-baseline biochemistry value based on CTC grade during consolidation and TFR phases (TFR Safey set) Study A2408

	Consolidation (NTCS)[1] N=126			TFR[2] N=126		
Parameter	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Alanine aminotransferase (U/L) (Hyper)	65 (51.6)	2 (1.6)	0	19 (15.1)	0	0
Albumin (g/L) (Hypo)	2 (1.6)	0	0	0	0	0
Alkaline phosphatase (U/L) (Hyper)	23 (18.3)	0	0	13 (10.3)	0	0
Aspartate aminotransferase (U/L) (Hyper)	55 (43.7)	1 (0.8)	0	14 (11.1)	0	0
Bilirubin (umol/L) (Hyper)	41 (32.5)	0	0	5 (4.0)	0	0
Calcium Corrected (mmol/L) (Hyper)	3 (2.4)	0	0	4 (3.2)	0	0
Calcium Corrected (mmol/L) (Hypo)	29 (23.0)	0	0	5 (4.0)	0	0
Creatinine (umol/L) (Hyper)	39 (31.0)	0	0	33 (26.2)	0	0
Magnesium (mmol/L) (Hyper)	3 (2.4)	0	0	0	1 (0.8)	0
Magnesium (mmol/L) (Hypo)	1 (0.8)	0	0	1 (0.8)	0	0
Phosphate (mmol/L) (Hypo)	41 (32.5)	4 (3.2)	0	6 (4.8)	1 (0.8)	0
Potassium (mmol/L) (Hyper)	11 (8.7)	1 (0.8)	0	10 (7.9)	0	0
Potassium (mmol/L) (Hypo)	1 (0.8)	0	0	0	0	0
Sodium (mmol/L) (Hyper)	3 (2.4)	1 (0.8)	0	3 (2.4)	0	0
Sodium (mmol/L) (Hypo)	2 (1.6)	0	0	1 (0.8)	0	0
Triacylglycerol lipase (U/L) (Hyper)	25 (19.8)	8 (6.3)	2 (1.6)	13 (10.3)	2 (1.6)	1 (0.8)
Uric acid (umol/L)	28 (22.2)	0	5 (4.0)	40 (31.7)	0	2 (1.6)

Study A2405 (ENESTcmr)

No patients had grade 3/4 hematology values at baseline and a few patients had new grade 3/4 abnormalities occurred during treatment.

Table 48 Newly occurring or worsening grade 3 or 4 haematological abnormalities (safety set) Study A2405

Hematological abnormality	Nilotinib N=101 n (%)	Imatinib N=103 n (%)
Hemoglobin	2 (2.0)	1 (1.0)
WBC count	0	3 (2.9)
Platelet count	0	3 (2.9)
Neutrophils total	2 (2.0)	7 (6.8)
Lymphocytes	1 (1.0)	1 (1.0)

The majority of grade 3/4 abnormalities were lipase increased (17.8% vs. 4.9% in nilotinib and imatinib, respectively) and decreased phosphate (11.9% vs. 16.5%).

Safety in special populations

Not applicable.

Safety related to drug-drug interactions and other interactions

There are no drug-drug interactions studies included in this submission.

Discontinuation due to adverse events

Study I2201 (ENESTfreedom)

The AEs leading to discontinuation were infrequent (4.7% of all the patients in the Safety set). The incidence of AEs leading to study drug discontinuation reported in the NTCS phase and the NTRI phase were 2.8% and 4.7%, respectively. The AEs leading to discontinuation reported in the NTCS phase were cardiac arrest, muscular weakness, cerebrovascular accident, agitation, eczema, xanthelasma, intermittent claudication, and peripheral arterial occlusive disease.

The AEs leading to discontinuation reported in the NTRI phase were coronary artery disease, uvulitis, chest pain, blood cholesterol increased, hyperglycemia, breast cancer, intermittent claudication, and peripheral arterial occlusive disease. The incidence of AEs requiring dose adjustment or interruption reported in the NTCS phase and the NTRI phase were 5.6% and 12.8%, respectively.

Study A2408 (ENESTop)

The AEs leading to discontinuation were infrequent (6.1% of all the patients in the Safety set). The incidence of AEs leading to study drug discontinuation reported in the NTCS phase and the NTRI phase were 3.1% and 7.8%, respectively. The AEs leading to discontinuation reported in the NTCS phase were acute myocardial infarction, cerebral infarction, arterial hemorrhage, hypertension, and peripheral arterial occlusive disease. The AEs leading to discontinuation reported in the NTRI phase were necrosis, hypercholesterolemia, adenocarcinoma, pleural effusion, and pleural fibrosis. The incidence of AEs requiring dose adjustment or interruption reported in the NTCS phase and the NTRI phase were 17.2% and 15.7%, respectively.

Study A2405 (ENESTcmr)

The proportion of patients reporting AEs leading to discontinuation of study drug was significantly higher in the nilotinib group (21 patients, 20.8%) compared to the imatinib group (7 patients, 6.8%). With the exception of lipase increased which was reported in two patients, all other preferred terms were reported in only one patient each. In the nilotinib group, 11 patients (10.9%) experienced a grade 3/4 event resulting in discontinuation of study drug. In the imatinib group, 5 patients (4.9%) were discontinued due to a grade 3/4 AEs. After crossover, 20 patients (43.5%) had an AE that required dose adjustment or dose interruption, of which 10 patients (21.7%) had a grade 3/4 event [Study A2405-Table 14.3.1- 4.1.2]. In 15 patients (32.6%) (7 patients grade 3/4) these events were suspected to be related to study drug.

Post marketing experience

The post-marketing experience with nilotinib was reviewed and reported by the MAH and discussed at CHMP on an ongoing basis during the last 11 PSURs /data cut-off: 31 Jan 2016).

Relevant publications containing important new safety information published during the reporting interval were retrieved from the three publicly accessible, bibliographic databases Medline, Embase and Biosis Previews. The search criteria was inclusive of pregnancy outcomes (including termination) with no adverse outcomes, use in pediatric populations, compassionate supply, named patient use, lack of efficacy, asymptomatic overdose, abuse or misuse, medication error where no AEs occurred, or "near misses" and important non-clinical safety results.

The results of the literature review did not reveal any important articles. Although there are multiple publications of musculoskeletal pain after imatinib discontinuation, there was a single presentation by Berger et al at ASH 2015 that reported two patients with musculoskeletal pain after nilotinib discontinuation.

Based on the review, except for the single oral presentation, there were no new or significant safety findings related to Tasigna published in the peer-reviewed scientific or made available as unpublished manuscripts during the reporting interval.

2.5.1. Discussion on clinical safety

The safety profile of nilotinib is well-known after many years on the market. In the current setting with TFR, the interesting issue is not the exposure in itself, but the opposite. Nonetheless, patients are exposed for considerable period before entering the TFR phase. The exposure and non-exposure (in TFR) are deemed appropriate to compare the safety, when patients are treated with nilotinib and when patient are in TFR.

In general, there are more AEs during the NTCS phase compared with the TFR phase, however, the number of Grade 3/4 AEs is similar between the two phases in the ENESTfreedom, while slightly higher in the NTCS phase in the ENESTop study. All AEs occurred with a lower or similar frequency in the TFR phase, except for AEs related to muscles and extremity pain. Musculoskeletal pain which included arthralgia, pain in the extremity, myalgia, bone pain and spinal pain are observed in CML patients, when TKIs are discontinued. This could be a withdrawal symptom. The MAH evaluated the published literature; most of the data are only short communications. The frequency ranged from 5% to 46%, the wide range may be due to differences in study design, outcome definitions etc., although about 1/3

of the patients had symptoms. The median time to first occurrence was 1-6 weeks (in the published literature) and 8.3 and 9.5 weeks in the ENESTfreedom and ENESTop trials respectively. The pains were easily manageable in the clinic, either resolved spontaneously or by using analgesics. The possible mechanism of musculoskeletal pain after TKI discontinuation is not clear. By reviewing the literature, the MAH referred to data, indicating that increased values of the circulating Platelet-Derived Growth Factor Receptor Beta (PDGFβ) were reported in patients who experienced musculoskeletal pain after TKI discontinuation. It is not clear if PDGFβ was the causative factor or rather a marker of pain in these patients. Another report hypothesized that the cKIT and PDGF might be involved.

Dose tapering was not allowed in the two trials. However the nilotinib treatment exposure data during the consolidation phase were similar in the patients with vs. patients without musculoskeletal pain in the TFR phase. Re-initiation of nilotinib treatment was only performed in case of molecular relapse and never in order to manage the musculoskeletal pain.

From a clinical point of view a discontinuation or interruption of TKI treatment is considered a benefit to the patients, provided that a treatment free period conveys no increased risk to the patient, the suggested criteria are used, and the patients are being closely monitored by BCR-ABL for a whole life time. Updated data from 96 weeks support the primary findings, however, further the MAH should collect and provide data on late relapses on a yearly basis from the ongoing studies ENESTfreedom and ENESTop (see Risk Management Plan). Risk of resistance (in TFR) is classified as potential risk in the risk management plan. Even during long-lasting TFR, persistent CML stem cells are detectable using genomic analyses, but currently the clinical implications of dormant yet detectable leukemic stem cells is unknown and an active area of research. Despite a growing body of evidence supporting the use of genomic PCR methods to detect patient-specific gene fusions, analysis of BCR-ABL at the DNA level has been limited and thus, detecting persistent CML stem cells using these methods do currently not trigger any change in the management of the disease. However, the MAH should collect data on gene signature in patients who relapse on TFR compared to patients who relapse on treatment and provide data on a yearly basis (see Risk Management Plan).

There seems to a higher likelihood of SAEs in the NTCS in ENESTop, but this is not the case in the ENESTfreedom. The number of SAEs is in general low, and no apparent pattern can be observed. There are very few deaths. However, there is no indication of increased risk of death during TFR.

With regard to AESIs, a similar pattern is observed in both studies: the most striking difference is seen with regard to fluid retention and musculoskeletal pain, where a considerable higher numbers are seen in the TFR phase. This seems to be a withdrawal symptom of TKIs in CML patients.

After discontinuation of Tasigna therapy within the framework of attempting treatment-free remission (TFR), patients may experience musculoskeletal symptoms more frequently than before treatment discontinuation, e.g., myalgia, pain in extremity, arthralgia, bone pain, spinal pain or musculoskeletal pain (SmPC, section 4.8).

In ENESTfreedom study with newly diagnosed patients with Ph+ CML in chronic phase (N=190), musculoskeletal symptoms were reported within a year of Tasigna discontinuation in 24.7% versus 16.3% within the previous year on Tasigna treatment (SmPC, section 4.8).

If a woman who is being treated with nilotinib is considering pregnancy, treatment discontinuation may be considered based on the eligibility criteria for discontinuing treatment. There is a limited amount of data on pregnancies in patients while attempting treatment-free remission (TFR). If pregnancy is planned during the TFR phase, the patient must be informed of a potential need to re-initiate treatment with Tasigna during pregnancy (SmPC section 4.6).

2.5.2. Conclusions on clinical safety

The safety profile of nilotinib is well known for many years. All AEs occurred with a lower or similar frequency in the TFR phase, except for AEs related to muscles and extremity pain. Musculoskeletal pain is observed in CML patients, when TKIs are discontinued, the mechanism is not clearly understood, but they were usually well manageable in the clinical setting.

It is fully acknowledged that otherwise discontinuation could be helpful in reducing the impact of adverse events.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 16 was acceptable.

However, following the SAG oncology held on the 5th of April 2017 and further discussion on the risk of developing resistance off-therapy, the CHMP requested the inclusion of 2 post-authorisation safety studies to the pharmacovigilance plan in order to collect and provide data on late relapses on a yearly basis from ongoing studies ENEST-op and ENEST-freedom and to collect and provide data on gene signature on patients that relapse on TFR compared to patients that relapse on treatment.

The aim of those 2 studies is to address the newly added safety concern "risk of resistance (in TFR)", which has been included as missing information.

The CHMP endorsed the Risk Management Plan version 19.1 with the following content:

Safety concerns

Table 49 Summary table of safety concerns (changes in red italic)

Important identified risks	QT prolongation Myelosuppression Cardiovascular events Significant bleeding Severe infections Hepatic transaminase and bilirubin elevations Pancreatitis, lipase and amylase elevations Fluid retention Blood glucose increased Blood cholesterol increased Use in patients with hepatic impairment Interaction with strong CYP3A4 inhibitors Interaction with strong CYP3A4 inducers Interactions with sensitive CYP3A4 substrates

	Interaction with Food
Important potential risks	Sudden death Cardiac failure Drug induced liver injury Reproductive toxicity/pregnancy Skin malignancy Interaction with P-gp inhibitors Interaction with drugs eliminated by CYP2C8, CYP2C9, CYP2D6 or substrates of UGT1A1, and P-gp and OCT1 transporters Interactions with drugs that may prolong the QT interval
Missing information	Pediatric patients Use in patients with renal impairment Patients with uncontrolled or significant cardiac disease Risk of resistance (in TFR)

Pharmacovigilance plan

Table 50 Ongoing and planned studies in the PhV development plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final Reports (planned or actual)
Questionnaire for study CAMN107A2001 Details about the methodology to evaluate the use of educational material as a risk minimization activity Category 3	To assess the effectiveness of educational material for physicians and patients	QT prolongation, pancreatitis, lipase and amylase elevations, hepatic transaminase and bilirubin elevations, cardiac failure, use in patients with hepatic impairment , Strong CYP3A4 inhibitors and inducers, patients with uncontrolled or significant cardiac disease, Drugs that may prolong the QT interval, interaction with food	Ongoing	Interim CSR submitted:18-Dec-2015
CAMN107A2203 (pediatric investigation plan) A multi-center, open label, non-controlled phase	To assess efficacy of nilotinib in pediatric patients with Ph+ CML CP resistant or intolerant to either imatinib or	To evaluate the safety of nilotinib in pediatric patients	Ongoing	Final CSR: Planned Sep-2020

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final Reports (planned or actual)
II study to evaluate efficacy and safety of oral nilotinib in pediatric patients with newly diagnosed Ph+ chronic myelogenous leukemia (CML) in chronic phase (CP) or with Ph+ CML in CP or accelerated phase (AP) resistant or intolerant to either imatinib or dasatinib. Category 3	dasatinib.			
Collect and provide data on late relapses on a yearly basis from the ongoing studies ENESTfreedom (CAMN107I2201) and ENESTop (CAMN107A2408) Category 3	Collect and provide data on late relapses on a yearly basis from the ongoing studies ENESTfreedom (CAMN107I2201) and ENESTop (CAMN107A2408)	Risk of resistance (in TFR)	Ongoing	Planned Q1 2021
Collect data on gene signature in patients who relapse on TFR compared to patients who relapse on treatment and provide data on a yearly basis Category 3	Collect data on gene signature in patients who relapse on TFR compared to patients who relapse on treatment and provide data on a yearly basis	Risk of resistance (in TFR)	Ongoing	Planned Q1 2021

Risk minimisation measures

Table 51 Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important identified risks		
QT prolongation	Wording in SmPC section 4.4 and 5.3	Educational material
Myelosuppression	Wording in SmPC section 4.2, 4.4 and 4.8	None
Cardiovascular events	Wording in SmPC section 4.4	Educational material
Significant bleeding	Wording in SmPC section 4.8	None
Severe infections	Wording in SmPC section 4.8	None
Hepatic transaminase and bilirubin elevations	Wording in SmPC section 4.2, 4.8 and 5.3	Educational material
Pancreatitis, lipase and amylase elevations	Wording in SmPC section 4.2, 4.4 and 4.8	Educational material
Fluid retention	Wording in SmPC section 4.4 and 4.8	Educational material
Blood glucose increased	Wording in SmPC section 4.2, 4.4 and 4.8	Educational material
Blood cholesterol increased	Wording in SmPC section 4.2, 4.4 and 4.8	Educational material
Use in patients with hepatic impairment	Wording in SmPC section 4.2 and 4.4	Educational material
Hepatitis B reactivation	Wording in SmPC section 4.4 and 4.8	DHPC
Interaction with strong CYP3A4 inhibitors	Wording in SmPC section 4.4 and 4.5	Educational material
Interaction with strong CYP3A4 inducers	Wording in SmPC section 4.4 and 4.5	Educational material
Interactions with sensitive CYP3A4 substrates	Wording in SmPC section 4.5	Educational material
Interaction with food	Wording in SmPC section 4.2, 4.4, 4.5 and 5.2	Educational material
Important potential risks		
Sudden death	Wording in SmPC section 4.4 and 4.8	None
Cardiac failure	Wording in SmPC section 4.8	Educational material
Drug induced liver injury	Wording in SmPC section 4.8	None
Reproductive toxicity/ pregnancy	Wording in SmPC section 4.6, 4.8 and 5.3	Educational material
Skin malignancy	Wording in SmPC section 5.3	None
Interaction with P-gp inhibitors	Wording in SmPC section 4.5	None
Interactions with drugs eliminated by CYP2C8,	Wording in SmPC section 4.5	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
CYP2C9, CYP2D6, or substrates of UGT1A1 and P-gp, OATP1B1 or OCT1 transporters		
Interaction with drugs that may prolong the QT interval	Wording in SmPC section 4.4 and 4.5	Educational material
Missing information		
Pediatric patients	Wording in SmPC section 4.2	None
Use in patients with renal impairment	Wording in SmPC section 4.2 and 4.8	None
Patients with uncontrolled or significant cardiac disease	Wording in SmPC section 4.2, 4.4 and 4.8	Educational material
Risk of resistance (in TFR)	Wording in SmPC section 4.2 and 4.4	None

2.7. Update of the Product information

Sections 4.2, 4.4, 4.6, 4.8, 5.1 and 6.6 of the SmPC have been updated based on the results of Studies CAMN107I2201 and CAMN107A2408. Particularly, a new warning with regard to special monitoring of Ph+ CML patients in chronic phase who have achieved a sustained deep molecular response has been added to the product information. The Package Leaflet has been updated accordingly. Additional changes to the labelling were implemented to comply with the latest QRD template version 10.

During the procedure the MAH withdrew the PI changes related to Study CAMN107A2405 (ENESTcmr) that were proposed as part of the application as the CHMP was of the view that it was not relevant for these data to be reflected in the SmPC.

2.7.1. User consultation

Not applicable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Study I2201 (ENESTfreedom) showed a rate of successful TFR at 48 weeks of 51.6% (95% CI: 44.2, 58.9). The majority of patients who lost MMR or discontinued the TFR phase did this early during the first 24 weeks of the TFR phase. The KM estimated TFS rate at 48 weeks is 53.1% (95% CI: 45.7, 59.9). In patients who lost MMR in the TFR phase, nilotinib re-treatment was started in 86 patients,

but one patient failed to regain MMR. The time to regain MMR was rapid with a KM estimated median time of 7.9 weeks (95% CI: 5.1, 8.0). No patient progressed to CML-AP/BC or had a haematological relapse of CML-CP.

In Study A2408 (ENESTop) the rate of successful TFR at 48 weeks was 57.9% (95% CI: 48.8, 66.7). The majority of patients who lost MMR or had a confirmed loss of MR4 did so during the first 24 weeks of the TFR phase. The KM estimated TFS rate at 48 weeks is 58.7% (95% CI: 49.6, 66.7). Fifty-one patients restarted treatment due to confirmed loss of MR4 or loss of MMR in the TFR phase, of whom 48 patients (94.1%) achieved again MR 4 or MR4.5. Three patients failed in regaining MR4.5. The time to regaining MR4 and MR4.5 was rapid: KM estimated median of 12.0 weeks (95% CI: 8.3, 12.7) and 13.1 weeks (95% CI: 12.4, 16.1) respectively. No patient progressed to CML-AP/BC.

Updated data from 96 weeks confirmed the findings at 48 weeks.

Uncertainty in the knowledge about the beneficial effects

There is a concern about the patients that did not respond adequately when re-exposed to nilotinib upon relapse. The MAH has not been able to identify any prognostic factors that could predict relapses and specifically not early relapses and, even more important, resistant relapses. Due to small numbers of late relapses, it was not possible to study the potential prognostic factors for early versus late relapses. The main concern is related to the risk of resistance development off therapy.

Based on the above, the CHMP concluded that the MAH should collect and provide data late relapses on yearly basis from ongoing studies ENEST-op and ENEST-freedom and should also collect data on gene signature on patients that relapse on TFR compared to patients that relapse on treatment on yearly basis (see Risk Management Plan).

Risks

Unfavourable effects

The safety profile of nilotinib is well-known after many years on the market no new or unexpected safety signals were observed during the use of nilotinib. In the current setting with TFR, the interesting issue is not the exposure in itself, but the opposite. Increasing rates of musculoskeletal pain after TKI discontinuation seems to be the most import new signal identified from trials ENEST freedom and ENESTop. This AE seems to be probably a class specific AE and was observed more frequently after nilotinib discontinuation than during treatment; however they were usually manageable in the clinical setting.

Uncertainty in the knowledge about the unfavourable effects

Musculoskeletal pain is observed in CML patients, when TKIs are discontinued. This could be a withdrawal symptom, but the mechanism behind is not clearly understood. Updated safety showed that the incidence of musculoskeletal pain is significantly reduced from 48 to 96 weeks. In addition, such symptoms were easily managed in the clinical setting, and they resolved either spontaneously or by using analgesics.

Taking into account that the introduction of specific TKIs like imatinib has tremendously improved the prognosis of CML, it is important not to jeopardise this benefit by discontinuation the treatment.

However, provided the use of the suggested eligibility criteria and careful monitoring the BCR-ABL levels for the whole life time, it is considered a safe and manageable procedure in at least some CML-CP patients.

The main concern is related to the risk of resistance development off therapy which is discussed above and reflected in the risk management plan.

Effects Table

Table 52 Effects Table for Tasigna studies ENESTfreedom and ENESTop (data cut-off: ENESTfreedom: 30-Nov-2015, ENESTop: 26-Nov-2015)

Effect	Short Description	Unit	Treatment (ENESTfreedom)	Treatment (ENESTop)	Uncertainties/ Strength of evidence	References
Favourable Effects						
TFR	ENESTfreedom: MMR rate at 48 weeks ENESTop: no loss of MMR or confirmed loss of MR4 within 48 weeks.	N (%)	98 (51.6)	73 (57.9)	ENESTfreedom: The lower limit of the 95%CI was below the pre-defined 50% cut-off. ENESTop: The lower limit of the 95%CI was above the pre-defined 10% cut-off.	
Unfavourable Effects						
			NTCS phase	**TFR phase**		
ENESTfreedom						
Arthralgia	incidence	%	8.4	12.1		
Pain in extremity			2.6	6.3		
Bone pain			2.1	4.2		
myalgia			1.1	4.7		
ENESTop						
Arthralgia	incidence	%	6.3	23.0		
Myalgia			3.1	12.7		
Bone pain			1.6	3.2		
Musculoskeletal pain			1.6	7.1		

Abbreviations: CI: confidence interval, MMR: major molecular response, MR 4.0: molecular response 4 log reduction from baseline, NTCS: nilotinib treatment consolidation phase, TFR: treatment- free remission

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Both ENESTfreedom and ENESTop showed that discontinuation of treatment with nilotinib should be considered in eligible Philadelphia chromosome positive (Ph+) CML patients in chronic phase who have been treated with nilotinib for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy.

After discontinuation of nilotinib therapy, patients may experience musculoskeletal symptoms more frequently than before treatment discontinuation, e.g., myalgia, pain in extremity, arthralgia, bone pain, spinal pain or musculoskeletal pain. However these symptoms were easily managed in the clinical setting, and they resolved either spontaneously or by using analgesics.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

The introduction of TKIs have changed the natural history of CML from being a life-threatening disease which could only be cured by an allogeneic haematopoietic stem cell transplantation with the risks it entail, to a chronic disease with practically a normal life expectancy. The patients are however often faced with life-long treatment with TKIs.

As seen by the data, about 50% of the patients stay in MMR and do not relapse, those who relapse do so within 24 weeks, and if patients are re-treated, deep durable remission can be achieved in the majority of patients for more than 90 weeks.

The CHMP considered the opportunity for TFR safe and interesting from a clinical perspective, making it possible to eliminate acute and chronic side effects due to TKIs, minimizing drug interactions and also making reproduction possible, without exposure to TKIs. Patients that enter the TFR phase seem to have withdrawal symptoms. These are manageable and mainly related to musculoskeletal pain. Notwithstanding, whilst the benefit of a treatment discontinuation are evident, ascertainment that a treatment free period conveys no increased risk to the patient is paramount. Several issues have been addressed. In the published literature, the vast majority of patients who needed re-treatment of TKI did so during the first year after discontinuation, and most commonly during the first 6 months after discontinuation. These data confirmed, that the patients responded well to re-treatment with TKI, with the vast majority achieving MMR in a timely manner and no patients has developed TKI resistance in TFR that was detected during TKI re-initiation. The data submitted, did not suggest the resistance mechanisms to be a consequence of the treatment-free interval. When multivariate analyses were performed for successful TFR at 24 weeks, with age, gender, duration of TKI treatment prior to study entry, and time since first MR4.5 until study entry, the MAH could not identify any prognostic factors that could predict relapses, and specifically not early relapses. Due to small numbers of late relapses, it was not possible to study the potential prognostic factors for early versus late relapses.

Published data on time to AP/BC in patients with poor control of CML are very limited, and confined to trials investigating TKIs in CML patients who did not have an optimal response /failure or intolerance to imatinib. Only a few patients progressed to AP/BC. The risk of progression to AP/BC is increased in CML patients receiving second line TKIs as compared to newly diagnosed patients. The question whether TKI-treated CML patients, including those with treatment discontinuation periods can be considered cured still need to be addresses by data generated over significantly longer periods than currently available. Even during long-lasting TFR, persistent CML stem cells are detectable using genomic analyses, but currently the clinical implications of dormant yet detectable leukemic stem cells is unknown and an active area of research. Despite a growing body of evidence supporting the use of genomic PCR methods to detect patient-specific gene fusions, analysis of BCR-ABL at the DNA level has been limited and thus, detecting persistent CML stem cells using these methods do currently not trigger any change in the management of the disease. However, inclusion of genomic analyses of those patients who discontinued successfully currently for 12 months should be considered in order to allow a better separation of patients who may have a higher relapse risk during the follow up.

The MAH initially proposed changes in sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC based on the

results from the three studies. However, the results from both ENESTfreedom and ENESTop do not justify a change in 4.1, but should be reflected in sections 4.2, 4.4, 4.6, 4.8 and 5.1 of the SmPC.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Update of sections 4.2, 4.4, 4.6, 4.8, 5.1 and 6.6 of the SmPC based on the results from:

- Study CAMN107I2201 (ENESTfreedom: A Phase II, single-arm study evaluating nilotinib treatment discontinuation (treatment-free remission (TFR)) in newly-diagnosed patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase (Ph+ CML-CP) who achieved a sustained deep molecular response;
- Study CAMN107A2408 (ENESTop): A Phase II, single-arm study evaluating nilotinib treatment discontinuation (treatment-free remission (TFR)) in patients with Ph+ CML-CP who achieved a sustained deep molecular response on nilotinib treatment after switching from imatinib treatment;
The Package Leaflet has been updated accordingly. Additional changes to the labelling were implemented in line with the latest QRD template version 10.
An updated RMP, version 19.1, was agreed during the procedure.

The group of variations leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Update of sections 4.2, 4.4, 4.6, 4.8, 5.1 and 6.6 of the SmPC based on the results from:

- Study CAMN107I2201 (ENESTfreedom: A Phase II, single-arm study evaluating nilotinib treatment

discontinuation (treatment-free remission (TFR)) in newly-diagnosed patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase (Ph+ CML-CP) who achieved a sustained deep molecular response;
- Study CAMN107A2408 (ENESTop): A Phase II, single-arm study evaluating nilotinib treatment discontinuation (treatment-free remission (TFR)) in patients with Ph+ CML-CP who achieved a sustained deep molecular response on nilotinib treatment after switching from imatinib treatment;
The Package Leaflet has been updated accordingly. Additional changes to the Labelling were implemented in line with the latest QRD template version 10.
An updated RMP, version 19.1, was agreed during the procedure.

Summary

For further information please refer to the published Assessment Report: Tasigna H-798-II-84-G-AR