21 March 2024
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Tasigna

Nilotinib

Procedure no: EMEA/H/C/000798/P46/056

Note

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

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1. Introduction

On 20 December 2023, the MAH submitted a completed paediatric study for Tasigna, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

Steps taken for the assessment	
Description	**Actual Date**
Start of procedure	22 Jan 2024
CHMP Rapporteur Assessment Report	16 Feb 2024
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	n/a
CHMP adoption of conclusions:	21 Mar 2024

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study No. CAMN107A2409 (hereafter referred to as A2409) - An open label, multi-center nilotinib roll-over protocol for patients who have completed a previous Novartis sponsored nilotinib study and are judged by the investigator to benefit from continued nilotinib treatment is a standalone study.

2.2. Information on the pharmaceutical formulation used in the study

Nilotinib was provided as 50 mg, 150 mg and 200 mg hard gelatin capsules

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- CAMN107A2409 (hereafter referred to as A2409) - An open label, multi-center nilotinib roll-over protocol for patients who have completed a previous Novartis sponsored nilotinib study and are judged by the investigator to benefit from continued nilotinib treatment is a standalone study.

Study A2409 enrolled a heterogenous patient population, which included 57 patients in total, of which 7 were pediatric patients (aged <18 years) and the study concluded on 07-Jul-2023 (LPLV). This study was a voluntary post-approval safety study, but not part of a pediatric investigation plan nor post-approval commitment.

The results of this study are now submitted to the EMA, as a standalone submission, in accordance with Article 46 of Regulation (EC) No 1901/2006, which requires submission of any MAH-sponsored study that involves use in a pediatric population of a medicinal product covered by a marketing

authorization, whether or not the study is conducted in compliance with an agreed pediatric investigation plan.

2.3.2. Short description of the medicinal product

Nilotinib (Tasigna®, AMN107) is a selective inhibitor of both wild-type and imatinib-resistant forms of the tyrosine kinase activity of the BCR-ABL oncoprotein both in cell lines and in primary Philadelphia-chromosome positive (Ph+) leukemia cells. BCR-ABL is a constitutively active tyrosine kinase and drives the pathology of chronic myelogenous leukemia, a myeloproliferative disorder characterized by a clonal expansion of hematopoietic stem cells expressing the BCR-ABL gene. The therapeutic concept of BCR-ABL tyrosine kinase inhibition is an effective treatment modality for Ph+ CML as inhibition of BCR-ABL kinase activity with nilotinib results in apoptosis of Ph+ CML cells.

Nilotinib is an oral TKI which is active against the tyrosine kinase activity of the BCR-ABL protein, the key oncogenic driver in Ph+ CML.

Tasigna is currently indicated for the treatment of:

- Adult and pediatric patients with newly diagnosed Ph+ CML in the chronic phase
- Adult patients with chronic phase and accelerated phase Ph+ CML with resistance or intolerance to prior therapy including imatinib
- Pediatric patients with chronic phase Ph+ CML with resistance or intolerance to prior therapy including imatinib

CHMP's comment:

The approved posology for paediatric patients in the Tasigna SmPC (4.2.) is:

Posology for Philadelphia chromosome positive CML paediatric patients

Dosing in paediatric patients is individualised and is based on body surface area (mg/m2). The recommended dose of nilotinib is 230 mg/m2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg). Different strengths of Tasigna hard capsules can be combined to attain the desired dose.

There is no experience with treatment of paediatric patients below 2 years of age. There are no data in newly diagnosed paediatric patients below 10 years of age and limited data in imatinib-resistant or intolerant paediatric patients below 6 years of age.

Furthermore the Tasigna SmPC includes this paragraph in 4.2:

Paediatric population The safety and efficacy of Tasigna in paediatric patients with Philadelphia chromosome positive CML in chronic phase from 2 to less than 18 years of age have been established (see sections 4.8, 5.1 and 5.2). There is no experience in paediatric patients below 2 years of age or in paediatric patients with Philadelphia chromosome positive CML in accelerated phase or blast crisis. There are no data in newly diagnosed paediatric patients below 10 years of age and limited data in imatinib-resistant or intolerant paediatric patients below 6 years of age.

2.3.3. Study rationale, study design and study results

The study design and rationale for Study A2409 are summarized in Table 2-1.

Table 2-1 Summary of study design

Purpose	The purpose of this study was to better characterize the long-term safety of nilotinib in patients who were on nilotinib treatment in Novartis-sponsored studies and were benefiting from the treatment as judged by the investigator.	
Primary objective and endpoint	**Objective** To evaluate long-term safety data (SAEs and AEs)	**Endpoint** Frequency and severity of AEs and SAEs
Secondary objective and endpoint	**Objective** To evaluate clinical benefit as assessed by the investigator	**Endpoint** Proportion of patients with clinical benefit as assessed by the investigator at scheduled visits
Study design	This was a multi-center, open-label, phase IV study. Patients who were enrolled in Novartis-sponsored nilotinib studies, had benefitted from treatment with nilotinib and fulfilled all requirements in the parent study could be enrolled into the current roll-over study. Patients returned to the study center on a quarterly basis (12 weeks ± 1 week) for scheduled visit. AEs (non-serious and serious AEs), clinical benefit assessment by investigator and study medication dispensing information were collected. The original protocol of the current roll-over study was designed to provide continuation of treatment with nilotinib for patients enrolled in nilotinib studies. Therefore, the original protocol did not require AEs (non-serious and serious AEs) to be collected into the clinical database and only required SAEs to be collected in the Novartis safety database throughout the study duration. The scheduled visit frequency was annually. However, feedback from health authorities stated that all AEs should be collected. To account for this, the protocol was amended in 2016 (Protocol amendment 3, PA 3), with the primary objective changed to assess long-term safety of nilotinib. Consequently, PA 3 started to require all AEs (non-serious and serious AEs) entered into the clinical database, in addition to the continued SAE collection into the Novartis safety database. At the same time, the scheduled visit frequency was increased from annually to quarterly, and the protocol was also amended to require an investigator assessment of clinical benefit for patients.	
Rationale	As mentioned above, the purpose of this study was to better characterize the long-term safety of nilotinib in patients who were on nilotinib treatment in Novartis-sponsored studies and were benefiting from the treatment as judged by the investigator. Novartis decided the parent studies which could transfer patients to the roll-over study. All objectives of the parent study had to be reached, and the parent study was to be in the process of being completed and reported. Patients transferred directly from parent studies and commenced treatment with nilotinib as soon as they were consented and met the inclusion criteria of the roll-over protocol. Patients continued to receive nilotinib until one of the following occurred: the patient was no longer benefiting from the treatment, unacceptable toxicity developed, consent was withdrawn, there was non-compliance with the protocol, the investigator felt it was no longer in the patient's best interest to continue nilotinib therapy, if pregnancy occurred or the patient's death.	

Study population	This study included both male and female, adult and pediatric patients, who were enrolled in Novartis-sponsored nilotinib studies, had benefitted from treatment with nilotinib and those who had fulfilled all requirements in the parent study. There was no sample size estimation carried out for this study.
Key inclusion criteria	• Patients enrolled in a Novartis-sponsored study, receiving nilotinib and those who had fulfilled all requirements in the parent study. • Patients currently benefiting from the treatment with nilotinib, as determined by the investigator. • Patients who demonstrated compliance, as assessed by the investigator, with the parent study protocol requirements. • Willingness and ability to comply with scheduled visits, treatment plans and any other study procedures. • Written informed consent obtained prior to enrolling in roll-over study. • If consent cannot be expressed in writing, it was formally documented and witnessed, ideally via an independent trusted witness.
Key exclusion criteria	• Patients were permanently discontinued from nilotinib treatment in the parent study due to unacceptable toxicity, non-compliance to study procedures, withdrawal of consent or any other reason. • Patients who participated in a Novartis sponsored combination trial where nilotinib was dispensed in combination with another study medication and patient is still receiving combination therapy. • Patients who were currently receiving treatment with any medications that had the potential to prolong the QT interval or inducing Torsade de Pointes and the treatment could not be either safely discontinued at least one week prior to nilotinib treatment or switched to a different medication prior to start of nilotinib treatment and for the duration of the study . • Pregnant or nursing (lactating) women • Women of child-bearing potential.
Study treatments	The starting dose of nilotinib should be the same as the last dose that was given in the parent study. After this, the dose of nilotinib was based on the investigator's judgement. The maximum dose of nilotinib was 800 mg/day. The regimen was daily, except if total daily dose was 600 mg, it was taken as 300 mg BID, if total daily dose was 800 mg, it was taken as 400 mg BID. The dose for the pediatric patients was calculated based on the body surface area.
Key efficacy assessments	Efficacy assessment consisted of clinical benefit of nilotinib treatment as per investigator assessment. The regular collection of investigator attestation of continued clinical benefit only started after PA 3.
Key safety assessments	Safety assessments consisted of collecting AEs (non-serious and serious AEs) with their severity, causal relationship to study drug and action taken on study drug, and deaths. All SAEs were collected in the Novartis safety database during the whole study period, AEs (non-serious and serious AEs) were collected in the clinical database after PA 3. Hepatitis B test was required after PA 3.
Data analysis	The statistical analysis was performed by Novartis personnel according to the planned analysis described in the protocol. SAS version 9.4 or higher was used in all analyses. For complete details, please refer to [Study A2409-CSR-Section 9.7].

2.3.3.1. Results

2.3.3.1.1. Recruitment

In total, 57 patients were transferred from the CML, ALL, GIST, and KIT mutated melanoma parent studies to this roll-over study. Of the total 57 patients enrolled and treated in the study, 7 patients were below 18 years of age; 4 patients were rolled over from CAMN107A2120 parent study and 3 patients from CAMN107A2203 parent study. Of these 7 patients, four patients completed the study as per the protocol and three patients discontinued the study (one patient due to disease progression and two patients as per physician decision).

2.3.3.1.2. Baseline data

Four pediatric patients (2 to < 12 years) and 3 adolescent patients (12 to < 18 years) were included. Two were female and five were male. Please refer to Table 2-2 for individual patient details.

Table 2-2 Baseline demographics of patients < 18 years of age

Patient code	Gender	Age category	Age (years)	Indication
[redacted]	[redacted]	Pediatric	[redacted]	resistant/intolerant Ph+ CML-CP
		Pediatric		resistant/intolerant Ph+ CML-CP
		Pediatric		refractory/relapsed Ph+ ALL
		Pediatric		resistant/intolerant Ph+ CML-CP
		Adolescent		resistant/intolerant Ph+ CML-CP
		Adolescent		resistant/intolerant Ph+ CML-CP
		Adolescent		resistant/intolerant Ph+ CML-CP

Source: [Study A2409-CSR Listing 16.2.4-1.1; Study A2120-CSR Listing 16.2.4-2.1; Study A2120-CSR Listing 16.2.4-2.3; Study A2203-CSR Listing 16.2.1-1.1]

2.3.3.1.3. Efficacy results

Country or Subdivision/ subject ID	Age / sex	Assessment date / study date	Visit	Investigator confirmation
[redacted]		03MAR2017/718	Visit 3	Yes
		25MAY2018/1166	Visit 8	Yes
		19APR2019/1495	End of Treatment	Yes
[redacted]		18MAY2018/1160	Visit 8	Yes
		03MAY2019/1510	End of Treatment	Yes
[redacted]		12MAY2017/682	Visit 4	Yes
		16JUL2018/1112	Visit 9	Yes
		08NOV2018/1227	End of Treatment	Yes
[redacted]		29APR2019/1	Enrollment	Yes
		14OCT2019/169	Visit 3	Yes
		27MAR2020/334	Visit 5	Yes
[redacted]		12OCT2020/533	Visit 7	Yes
		03JAN2021/616	Visit 8	Yes
		11JUL2022/1170	Visit 14	Yes
		27FEB2023/1401	End of Treatment	Yes

[redacted]	20OCT2017/1122	Visit 7	Yes
	10OCT2018/1477	Visit 11	Yes
	05JUL2019/1745	Visit 14	Yes
	09JUL2020/2115	Visit 18	Yes
	01JUL2021/2472	End of Treatment	Yes
[redacted]	26MAR2019/1	Enrollment	Yes
	24JUN2019/91	End of Treatment	No
[redacted]	25JUN2020/1	Enrollment	Yes
	26FEB2021/247	Visit 4	Yes
	13AUG2021/415	Visit 6	Yes
	11NOV2021/505	Visit 7	Yes
	28APR2022/673	Visit 9	Yes
[redacted]	09JUN2023/1080	End of Treatment	Yes

The clinical benefit data was collected only after protocol amendment 3 (PA 3). All the patients of the age below 18 years in the study had at least one clinical benefit assessment on study. All these patients were still benefiting from the study treatment at the end of treatment visit, except for one adolescent, female patient who discontinued due to disease progression.

CHMP's comment:

6 out 7 patients had resistant/intolerant Ph+ CML-CP and 1 patient had refractory/relapsed Ph+ ALL. All patients were deemed to have clinical benefit at least once per investigator assessment except. One patient had disease progression three months after enrolment.

It is supported that these limited clinical efficacy data warrants no changes to section 5.1. of the SmPC.

2.3.3.1.4. Safety results

All SAEs were collected in the Novartis safety database during the whole study period, however, AEs (non-serious and serious AEs) were only collected into the clinical database after PA 3 released in 2016, and AEs were not collected systematically until the patients signed the ICF associated with PA 3. Therefore, to present the safety data collected during the study in a comprehensive and transparent way, the SAE data from the Novartis safety database was analyzed, in addition to the data collected in the clinical database after PA 3. Based on the safety data collected in the clinical database, all the patients of the age below 18 years experienced AEs. Of note, none of the events were reported as serious and none of them led to permanent discontinuation of the study drug. All the events reported were of grade 1 or grade 2 severity, except for a grade 3 decreased appetite event in one patient, which was managed by a non-drug therapy. Except for alopecia and growth retardation which occurred in one patient each, and increased blood bilirubin and electrocardiogram QT prolonged which occurred in the same patient, none of the events were suspected to be related to the study drug by the investigator. None of the patients died during the study (Table 2-3).

Table 2-3 Summary of AEs in patients < 18 years of age

Patient code	Gender	Age (years)	Preferred terms	Grade	Outcome
[redacted]			Oropharyngeal pain	1/2	Recovered
			Tracheitis	1	Recovered
			Nasopharyngitis	2	Recovered
			Tracheobronchitis	2	Recovered
[redacted]			Rhinitis	1	Recovered
			Ear pain	2	Recovered
			Ear infection	2	Recovered
			Ligament sprain	2	Recovered
			Fatigue	2	Continuing[a]
			Poor quality sleep	1	Recovered
			Skin depigmentation	2	Recovered
[redacted]			Pyrexia	1	Recovered
			Lymphadenopathy	1	Recovered
			Diarrhoea	1	Recovered
			Asthma	2	Recovered
			Influenza	2	Recovered
			Alopecia	1	Recovered
			Pain in extremity	1	Recovered
			Dysphonia	1	Recovered
[redacted]			Constipation	2	Recovered
			Headache	1	Recovered
			Vitamin D decreased	1	Continuing[a]
			COVID-19	1	Recovered
			Arnold-Chiari malformation	1	Continuing[a]
[redacted]			Alanine aminotransferase increased	1	Recovered
			Blood phosphorus increased	1	Recovered
			Eosinophil count increased	1	Recovered
			Headache	1	Recovered
			Oropharyngeal pain	1	Recovered
			Abdominal pain upper	1	Recovered
			Pain in extremity	1	Recovered
			Growth retardation	2	Recovered
			Nasopharyngitis	1	Recovered
[redacted]			Decreased appetite	3	Recovered
[redacted]			Growth retardation	2	Continuing[a]
			Vitamin D deficiency	2	Recovered
			Blood bilirubin increased	2	Continuing[a]
			Electrocardiogram QT prolonged	1	Continuing[a]
			Rotavirus infection	1	Recovered

Source: [Study A2409 CSR Listing 16.2.7-1.1]
[a] Events which were continuing at the EOT visit

Based on the Novartis safety database, none of the pediatric patients experienced SAEs.

CHMP's comment:

Currently, the Tasigna SmPC includes these paragraphs in 4.8:

Paediatric population

The safety of nilotinib in paediatric patients (from 2 to <18 years of age) with Philadelphia chromosome positive CML in chronic phase (n=58) has been investigated in one main study over a period of 60 months (see section 5.1). In paediatric patients, the frequency, type and severity of adverse reactions observed have been generally consistent with those observed in adults, with the exception of hyperbilirubinaemia/blood bilirubin increase (Grade 3/4: 10.3%) and transaminase elevation (AST Grade 3/4: 1.7%, ALT Grade 3/4: 12.1%) which were reported at a higher frequency than in adult patients. Bilirubin and hepatic transaminase levels should be monitored during treatment (see sections 4.2 and 4.4).

Growth retardation in paediatric population

In a study conducted in the CML paediatric population, with a median exposure of 51.9 months in newly diagnosed patients and 59.9 months in imatinib/dasatinib-resistant or imatinib-intolerant Ph+ CML-CP patients, growth deceleration (crossing at least two main percentile lines from baseline) was observed in eight patients: five (8.6%) crossed two main percentile lines from baseline and three (5.2%) crossed three main percentile lines from baseline. Growth retardation related events were reported in 3 patients (5.2%). Close monitoring of growth in paediatric patients under nilotinib treatment is recommended (see section 4.4).

The observed AEs are generally in line with previous reported AEs for Tasigna and are in line with the current SmPC.

It is supported that this submission recommends no changes to the SmPC.

2.3.4. Discussion on clinical aspects

Study A2409 was conducted in adult and pediatric patients to characterize the long-term safety of nilotinib in patients who were on nilotinib treatment in Novartis-sponsored studies and were benefiting from the treatment as judged by the investigator. The safety profile of nilotinib in pediatric patient population with Ph+ CML-CP from 2 to less than 18 years of age have been established. There is no experience in pediatric patients below 2 years of age or in pediatric patients with Ph+ CML-AP or blast crisis. Data reported in this study are consistent with the known safety profile of nilotinib in the parent studies and other nilotinib clinical studies. No new safety signal or changes in the frequencies of known risks were identified in the pediatric patient population treated with nilotinib. Based on the results of Study A2409, the favorable benefit-risk profile of nilotinib in pediatric patients with CML remains unchanged.

Based on the results from Study A2409, no changes to the pediatric information of the current Tasigna SmPC are proposed.

CHMP's comment:

The MAH's conclusion is supported. The benefit-risk profile of nilotinib in its approved indication remains positive and no changes to the SmPC are required.

3. Overall conclusion and recommendation

The MAH's conclusion is supported. The benefit-risk profile of nilotinib in its approved indication remains positive and no changes to the SmPC are required.

☒ **Fulfilled:**

No regulatory action required.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report
An open label, multi-center nilotinib roll-over protocol for patients who have completed a previous Novartis sponsored nilotinib study and are judged by the investigator to benefit from continued nilotinib treatment	CAMN107A2409	7 July 2023	15 December 2023