17 October 2019
EMA/520858/2019
Committee for Medicinal Products for Human Use (CHMP)

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/P46/054

Note

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

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Table of contents

1. Introduction

Tasigna (nilotinib) 200 mg hard capsule was approved in the EU through the centralized procedure on 19-Nov-2007 for the treatment of chronic phase and accelerated phase Ph+ CML in adult patients resistant to or intolerant to at least one prior therapy including imatinib. Subsequently, Tasigna 150 mg hard capsule was approved in the EU on 20-Dec-2010 for the treatment of adult patients with newly diagnosed Ph+ CML in CP. More recently, on 15-Nov-2017 (Procedure EMEA/H/C/000798/X/0088/G), Tasigna was approved in the EU for the treatment of paediatric patients with newly diagnosed Ph+ CML in the chronic phase and paediatric patients with chronic phase Ph+ CML with resistance to or intolerance of prior therapy including imatinib. This approval was accompanied by the approval of new 50 mg hard capsule strength.

Tasigna was approved in Japan on 21-Jan-2009 for treatment of imatinib-resistant chronic myeloid leukemia in chronic or accelerated phase. Prior to the marketing approval in Japan, limited number of Japanese patients received Tasigna in clinical studies as part of Tasigna clinical development program. Therefore, the Pharmaceuticals and Medical Devices Agency required a conduct of a long-term observational study in Japanese patients to collect safety and efficacy data from all patients who received Tasigna after its launch in Japan (Post-approval measure). This observational study; CAMN107A1401, was an uncontrolled, open-label, multi-center, observational, post-marketing study in CML-CP or -AP adult and paediatric patients who received Tasigna as of 16-Feb-2009. A central registration system was adopted and all patients who received Tasigna were registered and followed for up to 3 year from the start of the administration of Tasigna. The registration period ended on 13-Jul-2015 and the end of investigation occurred on 18-Jan-2019. A total of 7 paediatric patients had been included in the study.

On 11 July 2019, the MAH submitted documentation for the stand-alone submission of the data of the 7 paediatric patients included in the CAMN107A1401 study, in order to adhere to the requirements of Article 46 of Regulation (EC) No1901/2006, as amended. A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study CAMN107A1401 is a stand-alone study

2.2. Information on the pharmaceutical formulation used in the study

Hard capsule in dosage strengths of 50 mg, 150 mg and 200 mg.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- CAMN107A1401 - an uncontrolled, open-label, multi-center, observational, post-marketing study in CML-CP or -AP adult and paediatric patients who received Tasigna as of 16-Feb-2009, conducted in Japan

2.3.2. Clinical study CAMN107A1401

Description

An uncontrolled, open-label, multi-center, observational, post-marketing study in CML-CP or –AP adult and paediatric patients who received Tasigna as of 16-Feb-2009, conducted in Japan

Methods

Objective(s)

The primary objective of this study was to investigate the safety and efficacy of Tasigna over long-term clinical use in patients with CML in chronic phase or accelerated phase.

Study design

An uncontrolled, open-label, multi-center, observational, post-marketing study in CML-CP or –AP adult and paediatric patients who received Tasigna as of 16-Feb-2009.

In order to collect the data on long-term safety and efficacy of Tasigna in Japan, a central registration system was adopted and all patients who received Tasigna from the start of the study (16-Feb-2009) were registered. CRFs of all patients who received Tasigna were screened from 418 sites by the end of investigation occurred on 18-Jan-2019.

Study population /Sample size

728 patients were included in the efficacy analyses and 928 patients (CML-CP or –AP adult and paediatric patients) were included in the safety analysis including seven paediatric patients. Of the seven paediatric patients, four were boys and three were girls.

Treatments

Tasigna was administered orally and was available as hard capsule in dosage strengths of 50 mg, 150 mg and 200 mg. The dose of Tasigna in paediatric patients was calculated based on body surface area (230 mg/m2 of Tasigna bid). The daily dose of Tasigna in paediatric patients ranged between 309.0 mg and 800.0 mg (mean daily doses).

Outcomes/endpoints

The primary objective of this study was to investigate the safety and efficacy of Tasigna over long-term clinical use in patients with CML in chronic phase or accelerated phase.

Results

Recruitment/ Number analysed

The numbers provided includes the entire study, and do not as such single out the paediatric population. Thus the table below is for the total population

Table 10-1 Numbers of investigation sites (medical institutions) and patients by founder (CRF-locked population)

Founder class	Founder	Number of medical institutions (%)		Number of patients (%)	
Total		418		988	
A	National/prefectural/city/private university hospitals	91	(21.77)	348	(35.22)
B	MHLW-established national hospitals	27	(6.46)	80	(8.10)
C	Prefectural/municipal hospitals	110	(26.32)	228	(23.08)
D	Public hospitals other than A-C	120	(28.71)	220	(22.27)
E	Corporate/private hospitals other than A-D	61	(14.59)	111	(11.23)
F	General practitioners/clinics	9	(2.15)	10	(1.01)

Demographic and other baseline characteristics

The majority of patients were men (56.25%) and 43.75% were females. Seven paediatric patients (<18 years) were included in this study (Table 2-1). All the paediatric patients (age range 7-15 years) were in CML-CP group (Table 2-1).

Table 2-1 Patient Demographics

Patient characteristics	Number of patients	Percentage
Total	928	
Males	522	56.25%
Females	406	43.75%
Age stratum II		
< 18 years	7	0.75%
≥ 18 years	920	99.14%
Unknown/ not specified	1	0.11%

Efficacy results

In the overall population

- The response rate (CHR) in the CML-CP hematologic response analysis population was 93.01%. Although it should be noted that the measures in this investigation are slightly different from the data at approval (Study 1101), the response rate was comparably high to the response rate at approval (CHR: 100%).
- The response rate in the CML-CP cytogenetic response analysis population (major CyR) was 75.45% (complete 66.82%, partial 8.64%). Because of different patient characteristics including the presence/absence of inclusion/exclusion criteria and a considerable number of patients not evaluable (81 patients), a simple comparison may not be appropriate. However, although the response rate was slightly lower than the response rate at approval (Study 1101) (major CyR: 93.8%, (complete 68.8%, partial 25.0%)), but the complete response rates were similar.
- The response rate (CHR, MR/NEL, RTC) in the CML-AP hematologic response analysis population was 68.52%. Although this investigation and the Japanese clinical study data are slightly different in terms of variables, the result was comparable to the response rate at approval (Study 1101) (CHR: 71.4%).

- The response rate in the CML-AP cytogenetic response analysis population (major CyR) was 50.98% (complete 39.22%, partial 11.76%). Because of different patient characteristics including the presence/absence of inclusion/exclusion criteria, a simple comparison may not be appropriate. However, the response rate in this investigation was higher than the response rate at approval (Study 1101) (Major CyR: 14.3%).

In the paediatric population (<18 years), the complete hematologic response (CML-CP) rate was 100.0%. The major cytogenetic response (CML-CP), a cytogenetic response measure, was also 100.0%.

Pediatrics (< 15 years)

In this investigation, 6 pediatric patients (< 15 years) were reported, all of whom had CML-CP. In the pediatric population, the complete hematologic response (CHR) rate was 100.0%. The major CyR, a cytogenetic response measure, was also 100.0% (relevant parts of Table 15-9 & Table 15-10 included below).

Pediatrics (< 18 years)

In this investigation, 7 pediatric patients (< 18 years) were reported, all of whom had CML-CP. In the pediatric population, the complete hematologic response (CHR) rate was 100.0%. The major CyR, a cytogenetic response measure, was also 100.0% (Table 15-9, Table 15-10).

CML-CP hematological effects of adult (over 18) was 92.93% (617/664 cases) and CML-CPcytogenetic effects of adult (over 18) was 75.15% (490/652 cases). There is no difference between pediatric and adult.

Table 15-9 Response rates by patient characteristic (hematologic response CML-CP)

Patient characteristics		No. of patients	Response			Test results	
			No. of patients	Proportion	Lower/upper limit of CI	Fisher's Exact	Mann-Whitney U
	Total	672	625	93.01%	90.81 , 94.82	-	-
Gender	Male	381	356	93.44%	90.47 , 95.71		
	Female	291	269	92.44%	88.78 , 95.20	p = 0.6488	-
Age stratum I	< 15 years	6	6	100.00%	54.07 , 100		
	≥ 15 years	665	618	92.93%	90.71 , 94.76	p = 1.0000	-
	Unknown/not specified	1	1	100.00%	2.50 , 100		
Age stratum II	< 18 years	7	7	100.00%	59.04 , 100		
	≥ 18 years	664	617	92.92%	90.70 , 94.75	p = 1.0000	-
	Unknown/not specified	1	1	100.00%	2.50 , 100		
Age stratum III	< 65 years	340	320	94.12%	91.06 , 96.37		
	≥ 65 years	331	304	91.84%	88.35 , 94.56	p = 0.2903	-
	Unknown/not specified	1	1	100.00%	2.50 , 100		
Age stratum IV	< 75 years	515	484	93.98%	91.56 , 95.87		
	≥ 75 years	156	140	89.74%	83.88 , 94.02	p = 0.0749	-
	Unknown/not specified	1	1	100.00%	2.50 , 100		

Table 15-10 Response rates by patient characteristic (cytogenetic response CML-CP)

Patient characteristics		No. of patients	Response			Test results	
			No. of patients	Proportion	Lower/upper limit of CI	Fisher's Exact	Mann-Whitney U
	Total	660	498	75.45%	71.99 , 78.69	-	-
Gender	Male	371	272	73.32%	68.51 , 77.75		
	Female	289	226	78.20%	72.99 , 82.82	p = 0.1714	-
Age stratum I	< 15 years	6	6	100.00%	54.07 , 100		
	≥ 15 years	653	491	75.19%	71.69 , 78.46	p = 0.3446	-
	Unknown/not specified	1	1	100.00%	2.50 , 100		
Age stratum II	< 18 years	7	7	100.00%	59.04 , 100		
	≥ 18 years	652	490	75.15%	71.65 , 78.43	p = 0.2031	-
	Unknown/not specified	1	1	100.00%	2.50 , 100		
Age stratum III	< 65 years	337	272	80.71%	76.09 , 84.79		
	≥ 65 years	322	225	69.88%	64.54 , 74.84	p = 0.0015	-
	Unknown/not specified	1	1	100.00%	2.50 , 100		
Age stratum IV	< 75 years	506	396	78.26%	74.41 , 81.78		
	≥ 75 years	153	101	66.01%	57.93 , 73.47	p = 0.0027	-
	Unknown/not specified	1	1	100.00%	2.50 , 100		

Safety results

In <u>the overall population</u>

- In the safety analysis population (928 patients), adverse reactions occurred in 720 patients and the incidence was 77.59% (720/928 patients), which was not higher than the incidence of adverse reactions at approval (97.06%; 33/34 patients) in Study 1101.
- Common adverse reactions were platelet count decreased in 14.01% (130/928 patients), blood bilirubin increased in 12.28% (114/928 patients), lipase increased in 9.91% (92/928 patients), hepatic function abnormal in 9.05% (84/928 patients), gammaglutamyltransferase increased in 8.84% (82/928 patients), anaemia in 8.30% (77/928 patients), rash in 7.97% (74/928 patients), alanine aminotransferase increased in 7.11% (66/928 patients), electrocardiogram QT prolonged in 6.79% (63/928 patients), white blood cell count decreased in 6.36% (59/928 patients) and blood glucose increased in 6.14% (57/928 patients).
- All of these common adverse reactions in this investigation were already observed by approval (Study 1101) and thus expected events in clinical use.
- The incidence of serious adverse reactions in this investigation was 20.26% (188/928 patients). Common serious adverse reactions were platelet count decreased in 5.06% (47/928 patients) and white blood cell count decreased in 2.16% (20/928 patients). This incidence of serious adverse reactions was not higher than the incidence at approval (Study 1101), which was 35.29% (12/34 patients). All of these common serious adverse reactions in this investigation were already observed by approval (Study 1101) thus expected events in clinical use.
- The incidences of adverse reactions of priority variables in this investigation were as follows: cardiac disorders in 11.75% (109/928 patients), electrocardiogram QT prolongation in 6.90% (64/928 patients), fluid retention in 8.94% (83/928 patients), interstitial lung disease in 1.29% (12/928 patients), rash in 18.21% (169/928 patients), haemorrhage in 0.86% (8/928 patients), infections in 3.02% (28/928 patients), worsening of hepatic impairment in 53.85% (35/65 patients) and worsening of renal impairment in 21.74% (25/115 patients).
- There was no issue to note about adverse reactions in patients with special characteristics (pediatrics, elderly, pregnant women, hepatic/renal impairment).

Of the seven paediatric patients in this study, five patients (71.4%) experienced adverse events. The incidence of adverse events in adults (≥18) was 77.6% (714/920 cases). One serious adverse event (acne pustular) was reported and no deaths were reported in paediatric patients. All the adverse events were suspected to be related to Tasigna. Based on the available data, no differences were observed in the safety profile of Tasigna in paediatric and adult patients in this study (CAMN107A1401) because most adverse events that occurred in paediatric were events that were generally observed in adults.

Pediatric patients (< 15 years)

In this investigation, 6 pediatric patients (< 15 years) were reported, of whom 4 patients had adverse reactions.

The following adverse reactions occurred: acne pustular, strabismus, hepatic function abnormal, jaundice, dry skin, rash, chest pain, blood creatine phosphokinase increased, electrocardiogram QT prolonged and hepatic enzyme increased in 16.67% (1/6 patients) each.

Pediatric patients (< 18 years)

In this investigation, 7 pediatric patients (< 18 years) were reported, of whom 5 patients had adverse reactions. The data on the occurrence of adverse events in the safety analysis population are shown in Table 15-6.

Table 15-6. List of adverse events that occurred under 18 years old

Age	Reason for use	Reason for use (detail)	Mean daily dose (mg)	Duration of treatment (day)	PT term	Seriousness	Seriousness (detail)	Number of days from the start of initial dose	Outcome	Number of days from date of start of event	Causality by physician	Memo
14	Chronic phase chronic myeloid leukaemia	Refractory imatinib	309.0	1079	Electrocardiogram QT prolonged	non-serious	-	29	Recovered	8	Yes	-
					Hepatic function abnormal	non-serious	-	113	Improved	57	Yes	-
					Jaundice	non-serious	-	113	Improved	57	Yes	-
					Dry skin	non-serious	-	78	Recovered	50	Yes	-
					Electrocardiogram QT prolonged	non-serious	-	186	Recovered	19	Yes	-
					Hepatic function abnormal	non-serious	-	277	Recovered	309	Yes	-
					Jaundice	non-serious	-	204	Improved	501	Yes	-
					Strabismus	non-serious	-	766	Not recovered	331	Yes	-

Age	Reason for use	Reason for use (detail)	Mean daily dose (mg)	Duration of treatment (day)	PT term	Seriousness	Seriousness (detail)	Number of days from the start of initial dose	Outcome	Number of days from date of start of event	Causality by physician	Memo
7	Chronic phase chronic myeloid leukaemia	Intolerance imatinib	400.0	1095	Hepatic enzyme increased	non-serious	-	8	Not recovered	85	Yes	-
					Hepatic enzyme increased	non-serious	-	120	Not recovered	57	Yes	-
					Hepatic enzyme increased	non-serious	-	274	Recovered	50	Yes	-
					Rash	non-serious	-	953	Improved	36	Yes	-
14	Chronic phase chronic myeloid leukaemia	Refractory imatinib	600.0	946	-	-	-	-	-	-	-	No adverse events occurred
11	Chronic phase chronic myeloid leukaemia	Intolerance imatinib	600.0	1095	-	-	-	-	-	-	-	No adverse events occurred
15	Chronic phase chronic myeloid leukaemia	Intolerance imatinib	507.1	183	Headache	non-serious	-	30	Recovered	71	Yes	-
					Liver disorder	non-serious	-	44	Recovered	71	Yes	-
					Rash	non-serious	-	44	Recovered	43	Yes	-
					Bone pain	non-serious	-	51	Recovered	148	Yes	-
14	Chronic phase chronic myeloid leukaemia	Refractory imatinib	600.0	367	Acne pustular	serious	hospitalizatio n	360	Improved	57	Yes	-
8	Chronic phase chronic myeloid leukaemia	Intolerance imatinib	400.0	123	Chest pain	non-serious	-	123	Recovered	2	Yes	-
					Blood creatine phosphokinase increased	non-serious	-	1	Recovered	158	Yes	-

Table 15-6. List of adverse events that occurred under 18 years old

Age	Reason for use	Reason for use (detail)	Mean daily dose (mg)	Duration of treatment (day)	PT term	Seriousness	Seriousness (detail)	Number of days from the start of initial dose	Outcome	Number of days from date of start of event	Causality by physician	Memo
14	Chronic phase chronic myeloid leukaemia	Refractory imatinib	309.0	1079	Electrocardiogram QT prolonged	non-serious	-	29	Recovered	8	Yes	-
					Hepatic function abnormal	non-serious	-	113	Improved	57	Yes	-
					Jaundice	non-serious	-	113	Improved	57	Yes	-
					Dry skin	non-serious	-	78	Recovered	50	Yes	-
					Electrocardiogram QT prolonged	non-serious	-	186	Recovered	19	Yes	-
					Hepatic function abnormal	non-serious	-	277	Recovered	309	Yes	-
					Jaundice	non-serious	-	204	Improved	501	Yes	-
					Strabismus	non-serious	-	766	Not recovered	331	Yes	-

Age	Reason for use	Reason for use (detail)	Mean daily dose (mg)	Duration of treatment (day)	PT term	Seriousness	Seriousness (detail)	Number of days from the start of initial dose	Outcome	Number of days from date of start of event	Causality by physician	Memo
7	Chronic phase chronic myeloid leukaemia	Intolerance imatinib	400.0	1095	Hepatic enzyme increased	non-serious	-	8	Not recovered	85	Yes	-
					Hepatic enzyme increased	non-serious	-	120	Not recovered	57	Yes	-
					Hepatic enzyme increased	non-serious	-	274	Recovered	50	Yes	-
					Rash	non-serious	-	953	Improved	36	Yes	-
14	Chronic phase chronic myeloid leukaemia	Refractory imatinib	800.0	946	-	-	-	-	-	-	-	No adverse events occurred
11	Chronic phase chronic myeloid leukaemia	Intolerance imatinib	600.0	1095	-	-	-	-	-	-	-	No adverse events occurred
15	Chronic phase chronic myeloid leukaemia	Intolerance imatinib	507.1	183	Headache	non-serious	-	30	Recovered	71	Yes	-
					Liver disorder	non-serious	-	44	Recovered	71	Yes	-
					Rash	non-serious	-	44	Recovered	43	Yes	-
					Bone pain	non-serious	-	51	Recovered	148	Yes	-
14	Chronic phase chronic	Refractory imatinib	600.0	367	Acne pustular	serious	hospitalizatio n	360	Improved	57	Yes	-

The following adverse reactions occurred: Hepatic enzyme increased (3 events), Jaundice, Electrocardiogram QT prolonged, hepatic function abnormal, Rash (each 2 events), Dry skin, Strabismus, Headache, Liver disorder, Bone pain, Acne pustular, Chest pain, Blood creatine phosphokinase increased (each 1 event). Only acne pustular was reported as serious event. 7 cases were reported in this study, and 71.43% (5/7 cases) occurred adverse events. The incidence of adverse events of adult (over 18) was 77.61% (714/920 cases). There is no difference between pediatric and adult, because most adverse events that occurred in pediatric were events that were generally observed even adult.

2.3.3. Discussion on clinical aspects

Study CAMN107A1401 was conducted in CML-CP or –AP adult and paediatric patients to characterize the safety and efficacy profile of Tasigna, in line with the approved marketing authorization in Japan.

The information provided in the clinical study report included the entire study population; safety analysis population consisted of 928 patients, and the efficacy analysis population consisted of 728 patients, i.e. adult and paediatric patients, and of these only 7 paediatric patients were included.

In this investigation, 7 pediatric patients (< 18 years) were reported, all of whom had CML-CP. In the pediatric population, the complete hematologic response (CHR) rate was 100.0%. The major CyR, a cytogenetic response measure, was also 100.0%. Compared to this the CML-CP hematological effects of adult (over 18) was 92.93% (617/664 cases) and CML-CPcytogenetic effects of adult (over 18) was 75.15% (490/652 cases). There is no difference between pediatric and adult.

Only one serious adverse event (acne pustular) was reported in a 14-year-old patient, the event was reported to be related to Tasigna as per physician's causality assessment. No new safety events were detected in the paediatric population treated with Tasigna. The safety profile observed in this study is consistent with the known and well characterized safety profile of Tasigna. The benefit risk assessment remains unchanged and positive.

3. CHMP's overall conclusion and recommendation

☒ 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: Tasigna Active substance: Nilotinib

Study title	Study number	Date of completion	Date of submission of final study report
Special drug use investigation for Tasigna® Capsules	CAMN107a1401	20 January 2019	4 July 2019