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

Votubia

everolimus

Procedure no: EMEA/H/C/002311/P46/028

Note

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

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Introduction

On 03.03.2016, the MAH submitted a completed paediatric study for everolimus, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

Scientific discussion

Information on the development program

The MAH stated that 'A Phase II Study of RAD001 in the Treatment of Patients with Plexiform Neurofibromas (PN) associated with Neurofibromatosis Type 1 (NF1)', study code CRAD001MIL04T, is a stand-alone study.

Information on the pharmaceutical formulation used in the study

Information as of CSR CRAD001MIL04T, a phase II trial conducted in Israel, imply that the pharmaceutical form used in the trial were 2.5 and 5 mg "everolimus tablets" ("supplied by Novartis at no charge"). Supposedly this means in terms of European products Votubia (but not Afinitor or Certican) 2.5 and 5 mg (normal) tablets.

For the product line Votubia also dispersible tablets, in effect resulting from a PIP, are available as a suitable paediatric formulation.

Clinical aspects

1. Introduction

The MAH submitted a final report for:

- CRAD001MIL04T, A Phase II Study of RAD001 in the Treatment of Patients with Plexiform Neurofibromas (PN) associated with Neurofibromatosis Type 1 (NF1)

2. Clinical study

CRAD001MIL04T, A Phase II Study of RAD001 in the Treatment of Patients with Plexiform Neurofibromas (PN) associated with Neurofibromatosis Type 1 (NF1)

Description

Following the clinical overview prepared for this submission, neurofibromatosis type 1 (NF1) is a common autosomal dominant disorder with an incidence of 1:3000 worldwide (>80 000 persons affected in the United States alone). Accordingly, NF1 is caused by a germline mutation in the NF1 tumor suppressor gene located on chromosome 17q11. Patients with Neurofibromatosis Type 1 (NF1) have an increased risk of developing tumors of the central and peripheral nervous system, including plexiform neurofibromas (PN), which are benign nerve sheath tumours that are among the most debilitating complications of NF1. These tumours are usually diagnosed early in life, may be multiple in number, and can grow throughout life, though early childhood is considered to be the period of

greatest risk for disease progression. There are no standard treatment options for PN other than surgery, which is often difficult due to the extensive growth and invasion of surrounding tissues.

Mammalian Target of Rapamcyin (mTOR) acts as a master switch of cellular catabolism and anabolism and controls protein translation, angiogenesis, cell motility, and proliferation. The NF1 tumour suppressor, neurofibromin, regulates the mTOR pathway activity, which is activated in NF1-deficent cells and tumours from NF1 patients.

Abrogating the activity of this pathway by inhibiting mTOR function reduces tumour proliferation in NF1 genetically engineered mouse models and human NF1-associated tumour explants.

Everolimus is an oral mTOR inhibitor that has been approved in several oncology and non-oncology indications, both in adults and in paediatric populations.

CHMP's comment:

This submission has been made in relation to the authorized product Votubia (but not Afinitor or Certican) presumably due to the disease investigated in trial CRAD001MIL04T. NF1, or PN associated with NF1, has several similarities with the two indications granted to Votubia in TSC (specifically SEGA and also similar pattern in renal AML), among them the inherited character, the growth kinetics of the (per se) benign, not metastasizing tumours during childhood and the involvement of the/a mTOR pathway.

It should, however, be noted that NF1 and TSC are genetically two clearly different diseases so that the submission does not relate to indications licensed to Votubia (or everolimus in general).

However it is clear that preclinical models provided the evidence of the hypothesis to be tested in trial CRAD001MIL04T, i.e. a mTOR inhibitor may be effective in NF1 since this pathway is genetically upregulated comparable to TSC.

Study CRAD001MIL04T was a local Novartis Israel sponsored study to explore everolimus in patients with Plexiform Neurofibromas (PN) associated with Neurofibromatosis Type 1 (NF1). The study aimed at evaluating the safety and efficacy of everolimus in two independent cohorts.

Furthermore, the clinical overview explains that its content presents paediatric data collected in study CRAD001MIL04T but the investigation of paediatric use was not a primary objective of study CRAD001MIL04T. The study was not powered for results based upon the paediatric subset and all data presented in this Critical Expert Overview are descriptive only.

Methods

- Objective(s)

Primary objective

1. To determine whether the mTOR inhibitor RAD001, administered orally daily on a continuous dosing schedule (1 course = 28 days):

   a. Increases **time to disease progression (TTP)** based on volumetric MRI measurements in children and adults with NF1 and inoperable progressive PN (**stratum 1**).

b. Results in **objective radiographic responses** based on volumetric MRI measurements in children and adults with NF1 and inoperable PN in the absence of documented radiographic progression at the study entry (**stratum 2**).

2. To evaluate the tolerability and toxicity of chronic RAD001 administration in this patient population as assessed by the NCI Common Toxicity Criteria, version 4.0

Exploratory objectives

1. To evaluate the clinical effect of RAD001 on clinical response as assessed by quality of life questionnaire including improvement in function or performance scale.
2. To evaluate the effect of RAD001 on skin lesions as assessed by digital photography.

- Study design

CRAD001MIL04T was a prospective phase II, single-arm, multicenter, open label, study, and designed to evaluate efficacy and safety of everolimus in children and adults with NF1-associated PN.

With the argument that the natural history of the growth of PN is unknown, it was planned to stratify the patient population as follows:

Stratum 1: Adults and children with NF1 and inoperable PN with the potential to cause significant morbidity with documented progressive PN prior to study entry.

Stratum 2: Adults and children with NF1 and inoperable PN with the potential to cause significant morbidity that do not have documented progression of the PN at time of study entry.

CHMP's comment:
This reason for the chosen stratification is not entirely clear to the CHMP since normally stratification is done for known prognostic factors. As long as documented progression is an unknown factor for the further curse of the disease it seems to be wiser to the CHMP not to stratify the trial and to have a single primary endpoint - for the question to be addressed the ORR seems to be optimal (which can occur in tumours having documented (recent) progression or not (see outcomes/endpoints below).

- Study population /Sample size

The protocol does not provide a sample size estimation.

The synopsis of the CSR simply states:

> *Approximately 20 patients were to be enrolled to receive everolimus in an open label manner. A total of 9 patients were enrolled to either Stratum 1 (N=4) or Stratum 2 (N=5).*

The **inclusion criteria** were partially differentiated by strata as follows:

Inclusion criteria for **all patients (stratum 1 and 2):**

1. Age: Patients must be ≥ 6 years of age at the time of study entry.

2. Clinically definite diagnosis of NF1 according to the NIH consensus conference criteria. In addition to a PN, one or more of the following diagnostic criteria for NF1 must be present:

a. Six or more café-au-lait spots (≥0.5 cm in prepubertal subjects or ≥1.5 cm in postpubertal subjects)

b. Freckling in the axilla or groin

c. Optic glioma

d. Two or more Lisch nodules

e. A distinctive bony lesion (dysplasia of the sphenoid bone or dysplasia or thinning of long bone cortex)

f. A first-degree relative with NF1

3. Patients must have PN that have the potential to cause significant morbidity, such as lesions that could compromise the airway or the great vessels, lesions that could cause nerve compression, lesions that could result in major deformity or significant cosmetic problems. Histologic confirmation of tumor is not necessary in the presence of consistent clinical and radiographic findings, but should be considered if malignant degeneration of a PN is clinically suspected.

4. Measurable disease; patient must have at least one measurable PN amenable to volumetric MRI analysis. For the purpose of this study, a measurable lesion will be defined as a lesion of at least 3 cm longest diameter measured in one dimension.

5. Prior therapy: patients who underwent a surgery for a PN will be eligible to enter the study after the surgery, provided the PN was incompletely resected and is measurable. Patients are eligible if complete resection of a PN is not feasible, or if a patient with surgical option refuses surgery.

- Patient may have been previously treated for a PN but must have fully recovered from any acute toxic effects of prior therapy
- Myelosuppressive chemotherapy: must not have received within 4 weeks prior to this study entry
- Biologic (anti-neoplastic agent): must not have received within 14 days of entry into this study
- XRT: ≥ 6 months from involved field radiation to index PN; ≥ 6 weeks from radiation to areas outside index PN
- Surgery: ≥ 2 weeks since undergoing any major surgery

6. Adequate hematological, renal, and hepatic functions as defined by:

Analyte	units
Hemoglobin	≥ 10 g/dL (following transfusion, if necessary)
Leukocyte count	≥ 2000/uL
Platelet count	≥ 100,000/uL
ALT	≤ 2.5 x the upper limit of normal
AST	≤ 2.5 x the upper limit of normal
Serum creatinine	≤ 1.5 x upper reference value
Bilirubin	≤ 1.5 x the upper limit of normal
Total Cholesterol	≤ 300 mg/dl or 7.75 mmol/L
Triglycerides	≤ 2.5 x the upper limit of normal (with lipid lowering drugs permitted)

7. If female and of child bearing potential, documentation of negative serum pregnancy test prior to enrollment. Sexually active pre-menopausal female patients (and female partners of male patients) must use adequate contraceptive measures, while on study.

8. Written informed consent. Parents (mother **and** father) or legal guardians must sign the informed consent form for patients under 18 years old and for patients with developmental delays, according to local guidelines.

Specific eligibility criteria stratum 1

Disease status: patients must have a documented progressive PN. Progression at the time of study entry is defined as:

- presence of new PN on MRI or CT, **OR**
- A measurable increase of the PN (≥ 20% increase in the volume, or a ≥ 13% increase in the total of the two longest perpendicular diameters or a ≥ 6% increase in the longest diameter) over the last two consecutive scans (MRI or CT) over the time period of approximately two years prior to evaluation for this study.
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Specific eligibility criteria stratum 2

Disease status: Patients with a **documented non-progressive PN** at time of study entry that do not fulfill the above mentioned definition for progressive PN.

The **exclusion criteria (both strata)** were the following:

1. Chronic treatment with systemic steroids or another immunosuppressive agent. Patient with endocrine deficiencies are allowed to receive physiologic or stress doses of steroids if necessary.

2. Evidence of an active optic glioma, malignant glioma, malignant peripheral nerve sheath tumor, or other cancer requiring treatment with chemotherapy or radiation therapy. Patients not requiring treatment are eligible for this protocol.

3. History of myocardial infarction, angina or stroke related to atherosclerosis

4. Clinically significant respiratory impairment / pulmonary disease

5. Pregnancy or breast feeding

6. Intercurrent infection at date of randomization

7. Prior history of organ transplant

8. Recent surgery (involving entry into a body cavity or requiring sutures) within the 2 weeks prior to randomization

9. Prior therapy with mTOR inhibitors (e.g.sirolimus, temsirolimus, everolimus)

10. Use of an investigational drug within the 12 weeks prior to randomization

11. Uncontrolled hyperlipidemia: Fasting serum cholesterol > 300 mg/dL OR > 7.75 mmol/L AND Fasting triglycerides > 2.5 x ULN

12. Uncontrolled diabetes mellitus as defined by fasting serum glucose > 1.5 x ULN

13. Patients with bleeding diathesis or on oral anti-vitamin K medication (except low dose warfarin)

14. Known diagnosis of human immunodeficiency virus (HIV) infection. HIV testing is not mandatory

15. Inability to attend scheduled clinic visits

16. For the purpose of MRI assessments the following exclude the pt:

    a. Ferromagnetic metal implants (e.g., braces, some types of aneurysm clips, shrapnel) unless approved as safe for use in MR scanner

    b. Uncontrollable claustrophobia or physically unable to fit into the machine (e.g., obesity, etc).

17. History of malignancy in the past two years, other than squamous or basal cell skin cancer.

- Treatments

The following are the statements of the protocol as to treatment(s):

> “The investigational drug used in the course of this trial is RAD001 (everolimus).
>
> For the duration of the study, RAD001 will be supplied by Novartis at no charge. The study drug will be administered by continuous oral daily dosing of one or more tablets.

Medication labels for study drug will comply with ICH/GCP and local regulatory requirements. Medication Labels will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

RAD001 is formulated as tablets of 2.5 and 5mg strength, blister-packed under aluminum foil in units of 10 tablets and dosed on a daily basis. RAD001 tablets should be opened only at the time of administration as drug is both hygroscopic and light-sensitive.

The Investigational Drug should not be stored above 30^0 C and must be protected from light and moisture."

In section 4.2 of the protocol, the following treatment plan has been displayed:

"Patients who meet the study eligibility criteria will receive RAD001 and will have their first daily dose of RAD001 on Day 1. The starting dose will be according to the following schedule:

The recommended starting dose of Everolimus is as follows:

Body Surface Area	Starting Daily Dose
≤ 1.2 m2	2.5 mg
1.3 m2 to 2.1 m2	5 mg
≥2.2 m2	7.5 mg

Titration may be required to obtain optimal therapeutic effect. Doses that are tolerated and effective vary between patients.

Everolimus whole blood trough concentrations should be assessed approximately 2 weeks after commencing treatment. Dosing should be titrated to attain trough concentrations of 5 to 15 ng/mL. If concentrations are below 5 ng/mL, the daily dose may be increased by 2.5 mg every 2 weeks, subject to tolerability.

The BSA in m^2 will be calculated using the following formula [(Weight in kilograms and Height in centimeters – Dubois & Dubois 1916] on an accurate height and weight measurements performed according to the following formula:

$$BSA = (W^{0.425} \times H^{0.725}) \times 0.007184$$

Dose adjustments will be permitted based on RAD001 trough blood levels and safety findings. A detailed explanation of permitted dose adjustments can be found in Section 6.3.2 "Permitted Study Drug Adjustments".

RAD001 will be administrated orally once daily, continuously with no rest period between courses with a glass of water after a meal, preferably at the same time every day.

Criteria for starting subsequent courses: a course may be repeated every 28 days if the patient has at least stable disease and again meets laboratory parameters as defined in the eligibility section."

CHMP's comment:

The dosing instructions for this trial resemble strongly the posology originally granted to Votubia in the indication TSC associated SEGA. This section (and thus the posology) has been further refined meanwhile by several variations. The recommended starting dose in SEGA is currently more uniform (than displayed in the table above) 4.5 mg/m^2 BSA (and 7 mg/m^2 in patients younger than 3 years).

The instructions for the duration of treatment differed slightly by stratum as follows:

"This study does not have fixed treatment duration. However, maximal duration for both strata is 24 months. A maximum number of courses were chosen to limit the chance for unacceptable toxicity in patients with **non-malignant** disease.

Stratum 1: Patients will be treated continuously until there is evidence of tumor progression as defined in section 7.5.2 or of unacceptable toxicity.

Stratum 2: Patients will be treated continuously to a maximum of 12 months of therapy. If an evidence of objective radiographic response during this time is observed – the treatment period will be extended to an additional 12 months of maximum response.

This maximum duration of treatment (12 months) was chosen to limit the chance for unacceptable toxicity in patients when there is no further evidence of benefit based on volumetric tumor measurements.

The maximal duration of the treatment in both strata is 24 months.

Patients will be followed for safety until 28 days after study treatment discontinuation."

- Outcomes/endpoints

The statistical sections, or the statistical considerations, of the trial are not really extensive. E.g, as just mentioned, a sample size estimation is missing in the protocol. Accordingly, the section "efficacy"

of the protocol contains a subsection "**Response Criteria",** which could be the endpoint of the primary objective for stratum 2. Specific explanations as to how the endpoint for the primary objective for stratum 1 (TTP) was precisely defined, cannot not be found in the protocol.

CHMP's *comment:*

The clinical overview submitted states:

"All 9 patients enrolled to study CRAD001MIL04T were included in the descriptive efficacy evaluation. A meaningful interpretation of the primary and exploratory objectives was not possible due to the limited number of patients enrolled to the study."

The same in terms of the synopsis of the CSR:

"Due to the limited data a meaningful interpretation of TTP is not possible."

Insofar it seems that the primary objective for stratum 1 was not (seriously) analysed. As just mentioned, the stratification of the planned (?) 20 patients to be recruited was an idea which the CHMP does not find convincing. In effect, only response, SD, and PD is (descriptively) reported for this trial.

- Statistical Methods

In essence none applied. Descriptive analyses presented. Statistical part of the protocol in essence limited to the definition of analysis populations (FAS, PPS, Safety population).

Results

Efficacy results (and baseline data) are displayed here in terms of the clinical overview since describing also result for the paediatric subpopulations:

- Recruitment/ Number analysed

  "All 9 patients enrolled to study CRAD001MIL04T were included in the descriptive efficacy evaluation. A meaningful interpretation of the primary and exploratory objectives was not possible due to the limited number of patients enrolled to the study."

CRAD001MIL04T.

- Baseline data

  "Of the 9 patients enrolled, 6 were paediatric, 5 were male and 4 were female."

Baseline data of the paediatric patients are summarized in the table 2-1 (as of the clinical overview) below: note, table not disclosed since it contains Commercially Confidential Information.

- Efficacy results

  "At data cut-off (26 April 2015) all patients had discontinued mainly because of completion of 12 months of treatment with everolimus. Eight patients, thereof 5 paediatric, demonstrated disease stabilization as best clinical response which did not meet the protocol defined criteria for continuation of treatment beyond 12 months. One adult patient was discontinued at physician's decision; hence disease stabilization was patient's best response after 12 months of treatment. One adult patient withdrew consent after having developed low grade vaginal bleeding, and one paediatric patient withdrew after the development of grade 3 mucositis. One paediatric patient discontinued treatment due to a serious adverse event with a short hospitalization due to an allergic reaction shortly after the initiation of the second cycle. Subsequently, after end of treatment this patient also demonstrated progression of PN.

  The descriptive analysis of the clinical response of treatment with everolimus demonstrated disease stabilization as best response, as assessed by local Investigator. SD was noted in 8 out of the 9 patients enrolled and treated within CRAD001MIL04T.

  Thereof SD was noted in 1 paediatric patient with NF1 related progressive PN at study entry (Stratum 1, patient 0102), and in all 4 paediatric patients (patient 0103, 0105, 0201, 0205 with NF1 related PN in whom the disease was stable at study entry (Stratum 2)). SD was ongoing for the duration of the planned study treatment of 12 months.

  Progressive disease was reported in 1 paediatric patient with NF1 related progressive PN after having been discontinued due to an SAE consisting of an allergic reaction with hospitalization shortly after the initiation of the second cycle of treatment with everolimus (Patient 0104, Stratum 1).

  Interpretation of the efficacy data from these 6 paediatric patients and the additional 3 adult patients is limited because of the overall low number of patients enrolled to study."

CHMP's comment:

The CSR concludes as to efficacy:

"Treatment with everolimus in patients with plexiform neurofibromas associated with neurofibromatosis type 1 resulted in modest clinical activity with disease stabilization as best response attained. … Considering the early discontinuation of the study efficacy results have to be interpreted with caution."

The clinical CHMP agrees with this overall conclusion. The unanswered question by this small phase II is whether this very modest (if any) clinical activity of a mTOR inhibitor can justify the long term treatment of this genetic disease with an obviously very slow growth or progression pattern, at least in the population investigated. The pattern of the consent withdrawal would argue that most patients (of stratum 1) decided to leave the trial, at least after 12 or more months of treatment, i.e. preferred no treatment of the not progressing, but also not responding, PN.

- Safety results

Safety results are displayed extensively in the CSR but can be reduced for this assessment report to the short description as of the clinical overview as follows:

“Overview

Adverse events (AE) were experienced by all patients in the study; all patients experienced at least one AE suspected to be related to everolimus. The AEs reported from study CRAD001MIL04T were consistent with the known everolimus safety profile. The most commonly reported AEs by preferred term in Stratum 1 were influenza like illness and headache; and headache in Stratum 2; all mostly grade 1 or 2. One AE of grade 3 mucositis was reported. Grade 4 AEs were not reported. Neither discontinuations due to AEs nor deaths during the study conduct were noted.

Adverse events causing study drug dose interruption or discontinuation,

Dose interruptions because of an AE (headache, flu-like symptoms, pneumonia, and abdominal pain, mostly low grade) occurred in 4 patients. There were no AEs that resulted in discontinuation from treatment with everolimus.

Serious adverse events

One serious adverse event was reported during the study. Patient 0104 (Stratum 1), a female patient with NF1 related progressive PN at baseline, 12.7 years of age, entered study CRAD001MIL04T with a known history of allergic reactions. The patient was started with a treatment of everolimus 5mg/daily on 12 March. This starting dose resulted in a Cmin of 2.0 ng/ml at visit 3 on 24 March 2013. At visit 4, on 09 April 2013, prior to the last administration of the treatment with everolimus on 14 April 2013, the patient showed a trough concentration of 5.2 ng/ml (target blood trough concentrations: 5–15 ng/mL).

On 15 March 2013 the patient developed itching in the hand that spread throughout the body and subsequently also developed a skin rash in the neck with breathing difficulties. Treatment with everolimus was halted and the patient was hospitalized for a two-day treatment with fenistil, prothiazine and steroids. The patient’s condition improved and gradually returned to baseline. Due to this event the patient was discontinued from further treatment with everolimus. However, also a progression of PN was found in scans performed shortly thereafter.

The investigator didn’t suspect a relationship between the event of allergic reaction and everolimus.

Deaths

No deaths were reported during the study or 28-day post treatment follow-up period.

Important safety risks

There were no important safety risks, as defined in the Afinitor®/Votubia® Risk Management Plan Version 10.0/ Version 9.0, reported during the study.

1. Discussion on clinical aspects

The clinical overview presents the following discussion:

A total of 9 patients were treated in study CRAD001MIL04T, 6 paediatric and 3 adult patients.

No objective responses were recorded in 9 patients with progressive or non-progressive NF1-associated PNs after treatment with everolimus, dosed once daily to achieve a target blood level of 5–15 ng/ml; stable disease was reported as best response in 8 patients and progressive disease in 1 patient.

The results of this study of everolimus in patients < 18years and >18 years old, confirm the acceptable safety profile of everolimus as shown by the reported frequency and severity of AEs, mostly of grade 1 and 2, with one AE of grade 3 (mucositis) reported and no treatment related serious adverse events.

The reported AE of mucositis grade 3 was consistent with the known safety profile of everolimus; it was medically managed by the investigator. Furthermore, no discontinuations due to adverse events except for 1 serious adverse event (allergic reaction, leading to treatment discontinuation) were reported. No deaths were reported during the study conduct.

Due to the limitations of the data, conclusions are descriptive only.

No changes to the paediatric information of the current Afinitor®/Votubia® (everolimus) Core Data Sheet are proposed as a result of this study, and no regulatory consequences of the submitted study are anticipated for the paediatric information in the European Summary of Product Characteristics (EU SmPC).

In conclusion, the benefit to risk relationship for everolimus remains positive for the currently approved indications and justifies continuation of the current development program in paediatric patients.

CHMP's overall conclusion and recommendation

Overall conclusion

The CHMP agrees with the discussion of the clinical overview of the MAH. It may be added that the modest, if any, activity of everolimus in this disease, NF1- associated PNs or NF1 in general is seemingly not a target for mTOR-inhibitor treatment as it is the genetic alteration causing TSC.

Recommendation

☒ **Fulfilled –**

No regulatory action required

Additional clarifications requested

Not applicable