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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/P46/026

Note

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

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Introduction

On July 08, 2015 the MAH submitted a Post-Marketing Surveillance (PMS) Study comprising also paediatric data in order to comply with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

1. Scientific discussion

1.1. Information on the development program

Following the MAH the newly submitted study CRAD001MKR20 was a local Korean Post-Marketing Surveillance (PMS) Study for everolimus in patients with Tuberous Sclerosis Complex (TSC)-associated subependymal giant cell astrocytoma (SEGA) and/or Renal Angiomyolipoma (AML). As this was a noninterventional study, efficacy evaluation was not mandatory, and the results were only collected if efficacy evaluation was performed under clinical practice conditions.

1.2. Information on the pharmaceutical formulation used in the study

The study report is written in Korean language. Following the synopsis in Englihs, Everolimus was formulated as tablets of 2.5mg, 5mg, and 10mg strengths for oral administration. Commercial product available on the local Korean market was used.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final CSR in Korean language. Following the synopsis in English language, the study report is for:

- Phase IV study CRAD001MKR20 entitled “Post-Marketing Surveillance (PMS) Study for Afinitor (everolimus) in patients with Tuberous Sclerosis Complex (TSC)-associated subependymal giant cell astrocytoma (SEGA) and/or Renal Angiomyolipoma (AML)” with the study dates first patient enrolled 14-Oct-2014 and last patient completed 26-Jan-2015.

1.3.2. Clinical study

study CRAD001MKR20 “Post-Marketing Surveillance (PMS) Study for Afinitor (everolimus) in patients with Tuberous Sclerosis Complex (TSC)-associated subependymal giant cell astrocytoma (SEGA) and/or Renal Angiomyolipoma (AML)”

Description

Study CRAD001MKR20 was an open-label, single center (Seoul National University Hospital, South Korea), single-arm, observational post-marketing surveillance (PMS) study.

Methods

Objective(s)

According to the synopsis, the objectives were to evaluate the safety and efficacy of everolimus in real-life conditions in its registered TSC indication(s) as requested by Ministry of Food and Drug Safety (MFDS), especially to identify the problems and questions associated with the following:

(1) Unknown adverse reactions, especially serious adverse reactions
(2) Incidence of adverse reactions under routine drug use
(3) Factors that may affect the safety of the drug
(4) Factors that may affect the effectiveness of the drug

Study design

This was an open-label, single centre study.

Study population /Sample size

Main inclusion criteria were:

- Patients with TSC-associated SEGA and/or with AML who require therapeutic intervention but are not candidates for curative surgical resection, and are designated the administration of the study drug in accordance with the locally approved “Dose & Administration” and “Precautions for Use”
- Patients who signed the informed consent form

Main exclusion criteria were:

- Patients with hypersensitivity to everolimus, to other rapamycin derivatives, or to any of the excipients
- Patients with hereditary problem of galactose intolerance, of Lapp lactase deficiency or of glucosegalactose

Following the synopsis, as to the sample size it was planned to include 5 patients, 3 analyzed patients out of which one patient was below 18 years old. Nor more details on sample size estimation can be derived from the documents (in English) submitted.

Treatments

Everolimus was formulated as
tablets of 2.5mg, 5mg, and 10mg strengths for oral administration. Commercial product available on the local Korean market was used. For treatment of TSC-associated SEGA, starting dose was determined based on Body Surface Area (see table below), dosing was to be titrated to attain trough blood concentrations of 5-10 ng/mL. Recommended initial dose of the study drug for TSC-associated AML was 10 mg once daily. Planned duration of treatment (and duration of study) was 12 weeks.

Body surface area (BSA)	Initial dose
≤ 1.2 m^2	2.5 mg once daily
1.3 m^2 ≤ BSA ≤ 2.1 m^2	5 mg once daily
≥ 2.2 m^2	7.5 mg once daily

Assessor’s comment:

Principles of the recommended initial dose as well as the method of dose titration of this trial are nearly identical with sec. 4.2 of the SmPC of Votubia after granting the first MA to Votubia in 2011. The current recommendation, however, provides a starting dose of 4.5 mg/m^2, thus, a higher and more individualised starting dose compared to the table above. The same has just been discussed within procedure EMEA/H/C/002311 P46 022.

Outcomes/endpoints

Following the synopsis (+/- the clinical overview) submitted, efficacy, safety and PK endpoints were as follows:

Efficacy:

As this was a non-interventional study, efficacy evaluation was not mandatory, and the results were only collected if efficacy evaluation was performed under clinical practice conditions.
SEGA response was defined as:

- Post-dose reduction of ≥ 30% in SEGA volume measured on brain image compared to baseline

AML response was defined as:

- Post-dose reduction of ≥ 50% in AML volume measured on renal image compared to baseline

Safety:
The safety evaluation consisted of monitoring and recording all adverse events including serious adverse events reported during study. If the study drug was discontinued during the study, adverse events/serious adverse events occurring within 4 weeks after discontinuation were to be reported. If the study drug continued to be used after the study period, patients were to be followed up for safety for up to 12 weeks after the study period, and only suspected serious adverse events in the investigator's judgment were to be reported to Novartis.

Bioanalytics:
As this was a non-interventional study, blood everolimus concentration and laboratory test was not mandatory, and the results were collected only if the blood everolimus concentration and laboratory test was performed under clinical practice conditions.

Statistical Methods

Analysis population consisted of all patients whose CRF had been completed and retrieved. Patients in the safety population consisted of all patients with CRF retrieved, who had received at least one dose of study drug and had completed at least one follow-up for safety (including phone, letter or e-mail). Patients in the efficacy population consisted of patients, among those in safety population, who had efficacy endpoint(s) measured. In this post-marketing surveillance, for TSC indication, only three patients (including one pediatric patient) were included in the safety population and one patient was included in the efficacy population. Therefore, statistical analysis for safety or efficacy was not conducted. The result of safety and efficacy evaluation and patient information including demographic information, medical/medication history and study drug administration status were presented in a narrative format.

Of the three patients included in safety evaluation, two patients who did not complete SEGA response and AML response were excluded and one patient was used for efficacy evaluation. For this patient, efficacy was evaluated by response of SEGA that was measured on post-dose brain image compared to pre-dose brain image (brain MRI or brain CT). Efficacy rate by factor was calculated, and factors that may have affected the efficacy rate were analyzed using categorical data analysis method (Chisquare test or Fisher's Exact test), etc.

As this observational study did not have a specific hypothesis to test, formal sample size calculation was not performed. No interim analysis was performed.

Results

Recruitment/ Number analysed

Three patients (2 adult males, 1 pediatric female) diagnosed with TSC-associated SEGA and/or with AML were treated at 1 center in South Korea. All 3 patients completed the 12-week study treatment.

Baseline data

Table 2-1 below as of the clinical summary provides some information on base-line demographic data as follows:

Table 2-1 Patient Demographics

Patient Number	100-M-001	100-M-002	100-M-003
Date of Birth (Age)	28-Jan-1992 (22)	24-Mar-1998 (16)	24-Jan-1992 (22)
Sex	Male	Female	Male
TSC Diagnosis	TSC-SEGA/ TSC-AML	TSC-SEGA/ TSC-AML	TSC-SEGA
Medical History	Angioembolization for AML	Craniotomy and tumor removal and EVD insertion	None
Current Medical Conditions	Seizure	Seizure	None
Concomitant Medications	Vigabatrin Clobazam Lamotrigine Topiramate Oxcarbazepine	Topiramate	Vitamin C Beecom C

Efficacy results

Of the 3 patients included in the safety evaluation, two patients who did not complete SEGA response and AML response were excluded and one patient was included in the efficacy evaluation. For this patient, brain imaging for SEGA response from 8 weeks to 12 weeks after the administration of study drug indicated that the patient had 'SEGA response' as defined per the study protocol. Brain or kidney imaging was not conducted during that timeframe and AML response was not assessed.

PK (PD) results

One patient had a dose increase based on their blood concentration level.

Safety results

During the study period, all patients received uninterrupted study drug for 12 weeks and no dose reductions occurred.

The safety results were consistent with the known safety profile of everolimus in TSC and no new safety concerns or unexpected findings were identified.
Overall, one patient reported an AE. The AE was Grade 1 stomatitis and the causality of study drug was 'possibly related' in the judgment of the investigator. Onset of this AE was on day 52 of treatment. The investigator treated the AE with Vitamin C and did not the change the patient's dose of everolimus. No Adverse Event was reported for the 16 years old pediatric patient enrolled in the study.

There were no SAEs or deaths reported during the study or during the follow up period.

1.3.3. Discussion on clinical aspects

The MAH/clinical overview discusses the clinical aspects of the submission of CSR MIC02:

> *"A total of 3 patients were treated in the study, 2 adult patients and 1 paediatric patient.*
>
> *The results of this study confirm the acceptable safety profile of everolimus as shown by the absence of serious adverse events and Grade 3 or 4 adverse events, albeit the small number of patients in this study. The reported event of stomatitis was consistent with the known safety profile of everolimus; it was medically managed by investigator. Furthermore, no discontinuations due to adverse events were reported and no deaths occurred during the study or the 12 week follow-up period.*

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 development program in paediatric patients."

The assessor agrees with this overall conclusion – and considers the overall paediatric information content of this CSR as minimal.

2. Rapporteur's overall conclusion and recommendation

Overall conclusion

Safety and efficacy finding of newly submitted study CRAD001MKR20 in (adult and paediatric) TSC patients with SEGA and/or AML are fully in accordance with result of study C2485 and M2301 already labelled. The benefit-risk of Votubia remains positive.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

3. Additional clarifications requested

n/a

4. Assessment of responses

n/a