21 May 2015
EMA/314770/2015
Procedure Management and Committees Support Division

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/P46/0022.1

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

© European Medicines Agency, 2015. Reproduction is authorised provided the source is acknowledged.

Introduction

On August 07, 2014 the MAH submitted a completed paediatric study in accordance 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

The MAH stated that study 'An open-label, multi-center, expanded access study of RAD001 in patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC). The EFFECTS STUDY: Everolimus For Fast Expanded aCcess in TSC SEGA' (EUDRACT No.: 2010-022583-13; CRAD001MIC02) was an expanded access study designed to provide access to everolimus to patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC), who were without satisfactory nonsurgical treatment alternatives, until the product was commercially available for this indication in the respective participating country or up to 31st December, 2013.

1.2. Information on the pharmaceutical formulation used in the study

Date of MA granted to Votubia 2.5 m tablets is 02/09/2011. Table 9-2 below provides details of the study medication of CRAD001MIC02.

Table 9-2 Study medication formulation and batch numbers

Study drug and strength	Formulation control number	Batch number
Everolimus 2.5 mg tablets	3747250.011	S0001-VMLK/2010-0380
	3747250.011	S0002-VMLK/2011-0513
	3747250.011	S0003-VMLK/2011-3200
	3747250.013	S0001-VMLK/2012-4138

According to the protocol, the daily dose should be taken at the same time every day either consistently with food or consistently without food. Everolimus should be swallowed whole with a glass of water and the tablets should not be chewed or crushed and grapefruit or citrus juices should be avoided. If the tablets cannot be swallowed, the tablets should be disintegrated in approximately 30 ml of water.

Assessor's comment:

Study initiation date was 28/03/2011, i.e. before granting a MA to Votubia in the EU. The dose instructions, nearly identical with the original label of Votubia 2.5, 5, and 10 mg tablets, as well as the dates clearly suggests that these 2.5 mg tablets investigated were 'normal' or 'non-dispersible' tablets. With procedure X/0008/G a line with 2, 3, and 5 mg dispersible tables have been added in 2013.

Thus, suitable paediatric formulations were, and are meanwhile, available.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for:

- Study eudract_number:2010-022583-13 (CRAD001MIC02) "An open-label, multi-center, expanded access study of RAD001 in patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC). The EFFECTS STUDY: Everolimus For Fast Expanded aCcess in TSC SEGA

1.3.2. Clinical study

Study 2010-022583-13 (CRAD001MIC02) "An open-label, multi-center, expanded access study of RAD001 in patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC). The EFFECTS STUDY: Everolimus For Fast Expanded aCcess in TSC SEGA

Description

Study CRAD001MIC02 was an open label, multicentre (44 centres all located within the EEA[1]) trial initiated in 2011 (first patient enrolled: 28-Mar-2011, last patient completed: 11-Mar-2014) investigating primarily safety of everolimus in TSC patients with SEGA in the context of an expanded access during the MA procedure for Votubia.

Methods

Objective(s)

According to the protocol primary objective was "*To evaluate safety of RAD001 in patients with SEGA associated with TSC.*" while Secondary objective "*To evaluate the investigator's best overall response rate of RAD001 in patients with SEGA associated with TSC.*"

Study design

This was an open-label, multi-center study designed to make everolimus available to patients with SEGA associated with TSC. The study was a non-comparative single arm trial.

Study population /Sample size

Main inclusion criteria were:

- Male or female of age 3 years or older
- Clinically definite diagnosis of tuberous sclerosis, according to the modified Gomez criteria
- Presence of at least one SEGA lesion identified by MRI or CT scan.

Main exclusion criteria were:

- Patients for whom SEGA-related surgery is required and planned
- List of concomitant diseases

[1] Belgium: 6 centers, Czech Republic: 1 center, France: 8 centers, Germany: 8 centers, Greece: 2 centers, Hungary: 2 centers, Italy: 12 centers, Poland: 1 center, Spain: 4 centers.

- List of (abnormal) laboratory parameters
- Prior participation in trial M2301 (a randomized controlled trial forming the major basis of the MA of Votubia in the indication SEGA)

As to the sample size estimation the protocol states that approximately of up to 250 patients were planned to be enrolled and that the sample size was not based on formal power considerations; rather it was based on feasibility (expected accrual rates, planned duration of the trial). The actual sample size may differ from this planned number.

Treatments

Everolimus was formulated as tablets of 2.5 mg strengths for oral administration. Oral daily doses were to be administered at the same time every day. Starting dose was determined based on body surface area (see table below), dosing was then titrated to attain trough blood concentrations of 5-15 ng/ml determined the first time 2 weeks after start of treatment.

Table 9-3 Recommended starting dose

Body Surface Area (BSA)	Starting daily dose
≤1.2 m^2	2.5 mg
1.3 to 2.1 m^2	5 mg
≥2.2 m^2	7.5 mg

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. Furthermore, current SmPC recommends earlier (than 2 weeks) determination of blood levels in children younger than 3 years (a population excluded in this trial).

All patients were treated with everolimus at a once daily oral dose until either:

- tumour progression (increase in SEGA volume determined by MRI)
- unacceptable toxicity (according to investigator's medical judgment)
- death
- discontinuation from the study for any other reason

or until the drug became commercially available for SEGA associated with TSC in the respective participating country or up to 31st December 2013. The latter limitation of treatment duration was already stated in the protocol.

Outcomes/endpoints

Efficacy: Tumor response and progression were assessed by MRI or CT scans of the brain (volume measurements of SEGA) at the investigators' discretion. Tumour assessments of measurable or non-measurabledisease/lesions were performed at screening and repeated at month 3, month 6, month 12 and annually thereafter and at discontinuation of the study drug. Best Overall Response was the Investigator's assessment of best radiological and clinical response during the study.

Safety: Safety assessments consisted of collecting Grade 3 or 4 adverse events (AEs) and laboratories abnormalities, and serious adverse events (SAEs). Grade 1 or 2 AEs were not to be reported, according to the protocol, unless they were significant for the investigator or caused a study drug dose modification or interruption. Adverse events were assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.0.

Pharmacokinetics: For the visits 3, 4, 5 and 6, the everolimus blood levels were summarized by visit.

All blood measurements were listed. Pre-dose trough blood samples for determination of everolimus concentration (C_{min}) were collected immediately prior to dosing starting on Visit 3 (Week 2). Blood samples for PK analysis were collected locally and sent to a central laboratory to perform the analysis.

Statistical Methods

There were no specific statistical hypotheses which were formally tested.

The investigator's best overall response was summarized with frequencies and percentages.

Descriptive statistics was used for PK data analysis.

No sample size or power calculations were performed. The proposed sample size of up to 250 patients was chosen based on the expected accrual rates and the planned duration of the trial; a total of 120 patients were finally enrolled in the study. No interim analyses were performed.

Results

Recruitment / Number analysed

The patient disposition (FAS [Full analysis set] population) is shown in Table 10-1.

Table 10-1 Patient disposition (FAS set)

	RAD001 N=120 n (%)
Patients	
Completed Study	100 (83.3)
Discontinued	20 (16.7)
Primary reason for premature discontinuation	
Adverse event(s)*	7 (5.8)
Other**	5 (4.2)
Subject withdrew consent	5 (4.2)
Abnormal laboratory value*	1 (0.8)
Administrative problems	1 (0.8)
SEGA progression	1 (0.8)

Source: Table 14.1-1.2

* The total number of patients with Adverse Event as primary reason of premature discontinuation were 8, including abnormal laboratory values.

** Other included Investigator's decision and Mother's decision

A total of 120 patients were treated in the study between 28 March 2011 and 30 June 2013 from 44 sites in 9 countries.

100 patients (83.3%) completed the study (i.e. they were moved to commercial drug or to local transition plans by 31st December 2013), 20 patients (16.7%) prematurely discontinued treatment, as summarized in Table 10-1 above.

Baseline data

Baseline demographic and disease characteristics of the study population (FAS set) are shown in tables 11-2 and 11-3 below.

Table 11-2 Demographic summary (FAS set)

Variable Statistic / Category	RAD001 N=120
Age (years)	
Mean	13.4
SD	9.15
Median	11.0
Range	1 – 47
Sex, n (%)	
Male	62 (51.7)
Female	58 (48.3)
Race, n (%)	
Caucasian	116 (96.7)
Asian	2 (1.7)
Native American	1 (0.8)
Other	1 (0.8)

Table 11-3 Disease characteristics (FAS set)

Variable Statistic / Category	RAD001 N=120
Time since TSC diagnosis (months)	
Mean	128.1
SD	83.53
Median	109.5
Range	2 – 368
Time since SEGA diagnosis (months)	
Mean	68.0
SD	71.18
Median	46.0
Range	0 – 288
Gomez criteria - major features, n (%)	
Facial angiofibromas or forehead plaques	93 (77.5)
Non traumatic ungual or periungual fibroma	18 (15.0)
Hypomelanotic macules (three or more)	95 (79.2)
Shagreen patch (connective tissue nevus)	47 (39.2)
Multiple retinal nodular hamartomas	23 (19.2)
Cortical tuber	106 (88.3)
Subependymal nodule	102 (85.0)
Subependymal giant cell astrocytoma	120 (100.0)
Cardiac rhabdomyoma, single or multiple	55 (45.8)
Lymphangiomyomatosis	2 (1.7)
Renal angiomyolipoma	59 (49.2)
Gomez criteria - minor features, n (%)	
Multiple, randomly distributed pits in dental enamel	6 (5.0)
Hemartomatous rectal polyps	0 (0.0)
Bone cysts	2 (1.7)
Cerebral white matter radial migration lines	16 (13.3)
Gingival fibromas	6 (5.0)
Non-renal hamartoma	3 (2.5)
Retinal achromic patch	4 (3.3)
'Confetti' skin lesions	15 (12.5)
Multiple renal cysts	19 (15.8)

Assessor's comment:

Since SEGA (in TSC patients) is a rare disease the patient characteristics at baseline are of note since they give some information on the natural course of SEGA: Median age at base-line of the patients was 11 years, median time since TSC diagnosis 9.1 years (109.5 months), and median time since SEGA diagnosis 3.8 year (46 months). Study MIC02 excluded patients younger than 3 years whereas study M2301 had no lower age limit. About 17% of the 117 patients recruited into study M2301 were

younger than 3 years demonstrating that SEGA occurs in patients younger than 3 years of age. The same can be seen in the lower age range of 1 year in table 11.2, representing obviously a protocol violation of study MIC02. In spite of these (early onset) data, trial MIC02 suggest that median time from TSC to SEGA diagnosis is longer than 5 years.

Efficacy results

The investigator's best overall response at the end of the study for the FAS population defined as best radiological and clinical response (radiological response in context with toxicities or other medical observations of the investigator) is shown in Table 11-4.

Table 11-4 Investigator's best overall response (FAS set)

Best response according to medical judgment	RAD001 N=120 n (%)
Complete response (CR)	0 (0.0)
Partial response (PR)	81 (67.5)
Stable disease (SD)	35 (29.2)
Progressive disease (PD)	1 (0.8)
Unknown	2 (1.7)
Not done	1 (0.8)

Assessor's comment

Response rate (or efficacy in general) was a secondary objective or trial MIC02 and should be considered, as actually determined, as "subjective best response" as judged by the local investigators. Median duration of study drug exposure was reported to be 396 days (ranging from 2 to 910 days). Taken into account that during this median study duration one progression and 2 unknown best responses were observed, however, it can stated that the overall pattern of the effect of everolimus on SEGA follows the overall result of trials C2485 and M2301 already assessed within the original MA, and the annual reassessments.

PK (PD) results

The trough (pre-dose) everolimus blood levels were evaluated for all patients at Week 2 (Visit 3). Everolimus blood levels were assessed at Week 4 (Visit 4), Week 6 (Visit 5) and Week 8 (Visit 6), only if drug dose was increased.

A summary of everolimus trough blood levels by visit for the FAS population is presented in Table 14.2-1.2.

Table 14.2-1.2 (Page 1 of 1)
Summary of everolimus plasma levels by visit
FAS set

Visit / Week	n	Mean	SD	CV (%)	Min	Median	Max	Geometric mean	Geometric CV (%)
Visit 3 / Week 2	109	4.06	2.873	70.81	0.70	3.20	17.90	3.28	73.41
Visit 4 / Week 4	87	4.89	2.937	60.06	1.00	4.30	17.00	4.12	66.07
Visit 5 / Week 6	57	5.01	3.171	63.34	1.10	4.30	16.50	4.20	65.19
Visit 6 / Week 8	65	5.27	3.011	57.10	1.20	4.60	17.80	4.57	58.47

The mean everolimus trough blood levels were below the desired range of 5-15 ng/ml at Week 2 (n= 109 patients, 4.06 ng/ml) and at Week 4 (n= 87 patients, 4.89 ng/ml), and in the desired range at Week 6 (n=57 patients, 5.01 ng/ml) and at Week 8 (n=65 patients, 5.27 ng/ml).

The correlation between everolimus blood level (ng/ml) and administered dose (mg) by visit has been analysed. A linear correlation between blood level and dose was observed only at Week 2 (Visit 3), while at Week 4, 6 and 8 no increase of blood levels was observed by increasing the dosage.

Assessor's comment

The interpretation of the PK data has limits. It is stated in the protocol that "*Trough blood samples (pre-dose) for trough RAD001 levels will be collected from all patients at week 2 (Visit 3). Samples at weeks 4, 6 and 8 only to be done if dose of RAD001 was increased. For the case of dose adjustments, RAD001 trough blood levels (pre-dose) will be assessed 1-2 weeks after any dose increase to a new level, or any decrease in an enzyme-inducing drug, or any increase in an enzyme-inhibiting drug.*" If sampling was actually implemented as stated in the protocol, table 14.2-1.2 would say that in 87 of a maximum of 109 (i.e. in at least 80%) patients dosing was increased after Visit3/first sampling Week2. If so, starting dose seems to be too low, a consideration which is further supported be a median of 3.2 (in a range of 0.7-17.9 ng/ml whereas the target range recommended was 5-15 ng/ml (as also in the current SmPC).

Furthermore, since starting dose is based on body surface one should expect **no** correlation in-between dose and c_{trough} levels. Actually, at first sampling (Week 2) a positive correlation was observed (as lower the dose as lower the blood levels), a correlation which was lost once dose was titrated (i.e. increased) according to Week 2 blood levels. This means in effect that as smaller the patient was in terms of body surface, as more likely it was, following the dose instructions for starting as outlined in table 9.3 above, that he will be underexposed by the starting dose recommendation.

Since the current SmPC recommends a more individualized starting dose of 4.5 mg/m^2, and dispersible tablets at the strength of 2, 3, and 5 mg are meanwhile available to implement this dose recommendation more precisely, result of study MIC02, thus, indirectly confirm that preceding discussions of the optimization of starting dose were justified.

Safety results

Extent of exposure in patients

The median daily dose of everolimus was 5.82 mg (range 2.0-11.8 mg), including days of temporary interruption of study drug.

Table 14.3-1.4 (Page 5 of 6)
Average daily dose of study drug in mg
Safety population

Visit window Average daily dose (mg)	RAD001 N=120 Including zero doses *	 Excluding zero doses **
Day 617 - 665		
n	38	37
Mean	6.62	6.89
SD	2.895	2.662
Min	0.0	2.5
Median	6.68	7.50
Max	12.5	12.5
Day 666 - 721		

The median duration of exposure for all the 120 patients was 395.5 days (range 2-910 days). Approximately half of the patients (57.5%) were exposed to everolimus for at least 48 weeks and one quarter (31.7%) for at least 88 weeks.

Table 12-1 Exposure to study drug (Safety population)

Variable Statistic/Category	RAD001 N=120
Duration of exposure, n (%)	
1 - 28 days	2 (1.7)
29 - 56 days	1 (0.8)
57 - 112 days	6 (5.0)
113 - 168 days	13 (10.8)
169 - 224 days	7 (5.8)
225 - 280 days	12 (10.0)
281 - 336 days	10 (8.3)
337 - 392 days	9 (7.5)
393 - 448 days	9 (7.5)
449 - 504 days	2 (1.7)
505 - 560 days	6 (5.0)
561 - 616 days	5 (4.2)
617 - 665 days	16 (13.3)
666 - 721 days	8 (6.7)
> 721 days	14 (11.7)
Duration of exposure (days)	
Mean	426.1
SD	239.34
Median (Min- Max)	395.5 (2 - 910)

Duration of exposure = date of last drug intake - date of first drug intake + 1.
Duration of exposure includes periods of temporary interruption of study drug.
Source: Tables 14.3-1.1

Study drug dose was reduced in 45 patients (37.5%). The reasons for dose reduction were: adverse event (34 patients), as per protocol (PK level) (5 patients), laboratory test abnormality (4 patients), dosing error (2 patients), scheduling conflict (1 patient), other (7 patients). Study drug was temporarily interrupted in 35 patients (29.2%). The reasons for dose interruption were: adverse event (27 patients), laboratory test abnormality (3 patients), scheduling conflict (1 patient), and other (7 patients). Study drug was prematurely discontinued in 20 patients (16.7%).

Concomitant medication

Overall, 113 patients (94.2%) received concomitant medications in any ATC class after start of study drug.

The most commonly used ATC drug classes were: antiepileptics (78 patients, 65.0%), antibacterial for systemic use (68 patients, 56.7%), ophtalmologicals (53 patients, 44.2%), analgesics (48 patients, 40.0%), stomatological preparations (48 patients, 40.0%), anti-inflammatory and antirheumatic products (33 patients, 27.5%).

Adverse events regardless of study-drug relationship

The overall incidence of adverse events was 74.2% (89 patients).

Table 12-2 Number of patients with adverse events, overall and by system organ class (Safety population)

	RAD001 N=120 n (%)
Patients with any AE(s)	89 (74.2)
System organ class	
Infections and infestations	51 (42.5)
Gastrointestinal disorders	40 (33.3)
General disorders and administration site conditions	26 (21.7)
Nervous system disorders	16 (13.3)
Metabolism and nutrition disorders	15 (12.5)
Respiratory, thoracic and mediastinal disorders	13 (10.8)
Investigations	11 (9.2)
Skin and subcutaneous tissue disorders	11 (9.2)
Reproductive system and breast disorders	8 (6.7)
Injury, poisoning and procedural complications	5 (4.2)
Eye disorders	4 (3.3)
Renal and urinary disorders	4 (3.3)
Blood and lymphatic system disorders	3 (2.5)
Vascular disorders	3 (2.5)
Cardiac disorders	2 (1.7)
Hepatobiliary disorders	2 (1.7)
Musculoskeletal and connective tissue disorders	2 (1.7)
Endocrine disorders	1 (0.8)
Immune system disorders	1 (0.8)
Psychiatric disorders	1 (0.8)

All AEs starting after first dose but not later than 28 days after last dose were analyzed.
Source: Table 14.3.1-1.1

The most common adverse events, reported in ≥ 5% of patients, were aphthous stomatitis, stomatitis, mouth ulceration, pyrexia, bronchitis, cough, diarrhea, headache and sinusitis.

Patients with any adverse event of Grade 3 or 4 were 28 (23.3%): 25 patients with AEs of Grade 3 and 3 patients with AEs of Grade 4. The most frequent adverse event of Grade 3 was stomatitis (4 patients, 3.3%). All the other AEs of Grade 3 or 4 were reported in one to 2 patients.

In the paediatric sub-population (90 patients age <18 years), the overall incidence of adverse events was 74.4% (67 patients). The most common adverse events reported (≥ 5% of patients) were pyrexia (16 patients, 17.8%); aphthous stomatitis (13 patients, 14.4%); bronchitis (11 patients, 12.2%); stomatitis (7 patients, 7.8%); sinusitis (6 patients, 6.7%); pharyngitis, pneumonia, diarrhoea, mouth

ulceration, cough, pneumonitis (5 patients, 5.6%). Patients with any adverse event of Grade 3 or 4 were 23 (25.5%): 21 patients (23.3%) with AEs of Grade 3 and 2 patients (2.2%) with AEs of Grade 4.

The most frequent AE (reported in > 2% of patients) of Grade 3 was stomatitis (4 patients, 4.4%). All the other AEs of Grade 3 or 4 were reported in one patient each.

Table 14.3.1-1.1a (Page 1 of 9)
Number of patients with adverse events, by primary system organ class and preferred term - age <18 years
Safety population

Primary system organ class Preferred term	RAD001 N=90 n (%)
Any primary system organ class - Total	67 (74.4)
Infections and infestations - Total	39 (43.3)
Bronchitis	11 (12.2)
Sinusitis	6 (6.7)
Pharyngitis	5 (5.6)
Pneumonia	5 (5.6)
Gastroenteritis	4 (4.4)
Nasopharyngitis	4 (4.4)
Otitis media	4 (4.4)
Upper respiratory tract infection	4 (4.4)
Acute tonsillitis	2 (2.2)
Ear infection	2 (2.2)
Gastroenteritis viral	2 (2.2)
Respiratory tract infection	2 (2.2)
Rhinitis	2 (2.2)
Viral infection	2 (2.2)
Bronchitis viral	1 (1.1)

Table 14.3.1-1.1a (Page 2 of 9)
Number of patients with adverse events, by primary system organ class and preferred term - age <18 years
Safety population

Primary system organ class Preferred term	RAD001 N=90 n (%)
Infections and infestations	
Bronchopneumonia	1 (1.1)
Cellulitis orbital	1 (1.1)
Eye infection	1 (1.1)
Giardiasis	1 (1.1)
Haemophilus infection	1 (1.1)
Infection	1 (1.1)
Influenza	1 (1.1)
Kidney infection	1 (1.1)
Laryngitis	1 (1.1)
Localised infection	1 (1.1)
Lung infection	1 (1.1)
Paronychia	1 (1.1)
Sepsis	1 (1.1)
Tonsillitis	1 (1.1)
Tooth infection	1 (1.1)
Urinary tract infection	1 (1.1)
Varicella	1 (1.1)
Viral skin infection	1 (1.1)

Table 14.3.1-1.1a (Page 3 of 9)
Number of patients with adverse events, by primary system organ class and preferred term - age <18 years
Safety population

Primary system organ class Preferred term	RAD001 N=90 n (%)
Gastrointestinal disorders	
- Total	30 (33.3)
Aphthous stomatitis	13 (14.4)
Stomatitis	7 (7.8)
Diarrhoea	5 (5.6)
Mouth ulceration	5 (5.6)
Abdominal pain	3 (3.3)
Vomiting	3 (3.3)
Constipation	1 (1.1)
Gingival bleeding	1 (1.1)
Gingival ulceration	1 (1.1)
Nausea	1 (1.1)
Tongue blistering	1 (1.1)
General disorders and administration site conditions	
- Total	20 (22.2)
Pyrexia	16 (17.8)
Fatigue	2 (2.2)
Local swelling	2 (2.2)

Table 14.3.1-1.1a (Page 4 of 9)
Number of patients with adverse events, by primary system organ class and preferred term - age <18 years
Safety population

Primary system organ class Preferred term	RAD001 N=90 n (%)
General disorders and administration site conditions	
Mucosal inflammation	2 (2.2)
Hyperpyrexia	1 (1.1)
Irritability	1 (1.1)
Oedema	1 (1.1)
Respiratory, thoracic and mediastinal disorders	
- Total	11 (12.2)
Cough	5 (5.6)
Pneumonitis	5 (5.6)
Acute respiratory failure	1 (1.1)
Bronchial obstruction	1 (1.1)
Dysphonia	1 (1.1)
Lung disorder	1 (1.1)
Pneumonia aspiration	1 (1.1)
Respiratory tract inflammation	1 (1.1)
Nervous system disorders	
- Total	9 (10.0)
Headache	3 (3.3)
Convulsion	1 (1.1)

Table 14.3.1-1.1a (Page 5 of 9)
Number of patients with adverse events, by primary system organ class and preferred term - age <18 years
Safety population

Primary system organ class Preferred term	RAD001 N=90 n (%)
Nervous system disorders	
Epilepsy	1 (1.1)
Hemiparesis	1 (1.1)
Hemiplegia	1 (1.1)
Hydrocephalus	1 (1.1)
Narcolepsy	1 (1.1)
Partial seizures	1 (1.1)
Somnolence	1 (1.1)
Status epilepticus	1 (1.1)
Skin and subcutaneous tissue disorders	
- Total	7 (7.8)
Rash	3 (3.3)
Acne	1 (1.1)
Neurodermatitis	1 (1.1)
Pityriasis rosea	1 (1.1)
Skin hyperpigmentation	1 (1.1)
Metabolism and nutrition disorders	
- Total	6 (6.7)
Abnormal weight gain	1 (1.1)

Table 14.3.1-1.1a (Page 6 of 9)
Number of patients with adverse events, by primary system organ class and preferred term - age <18 years
Safety population

Primary system organ class Preferred term	RAD001 N=90 n (%)
Metabolism and nutrition disorders	
Decreased appetite	1 (1.1)
Dehydration	1 (1.1)
Feeding disorder	1 (1.1)
Hypercholesterolaemia	1 (1.1)
Hypokalaemia	1 (1.1)
Injury, poisoning and procedural complications	
- Total	5 (5.6)
Ankle fracture	1 (1.1)
Foot fracture	1 (1.1)
Hand fracture	1 (1.1)
Near drowning	1 (1.1)
Subdural haematoma	1 (1.1)
Eye disorders	
- Total	4 (4.4)
Conjunctivitis	2 (2.2)
Asthenopia	1 (1.1)
Periorbital oedema	1 (1.1)

Table 14.3.1-1.1a (Page 7 of 9)
Number of patients with adverse events, by primary system organ class and preferred term - age <18 years
Safety population

Primary system organ class Preferred term	RAD001 N=90 n (%)
Investigations	
- Total	4 (4.4)
Blood creatine phosphokinase increased	3 (3.3)
Liver function test abnormal	1 (1.1)
Reproductive system and breast disorders	
- Total	4 (4.4)
Menstruation irregular	3 (3.3)
Amenorrhoea	2 (2.2)
Adnexal torsion	1 (1.1)
Dysmenorrhoea	1 (1.1)
Menorrhagia	1 (1.1)
Blood and lymphatic system disorders	
- Total	3 (3.3)
Eosinophilia	1 (1.1)
Lymphadenopathy	1 (1.1)
Neutropenia	1 (1.1)

Table 14.3.1-1.1a (Page 8 of 9)
Number of patients with adverse events, by primary system organ class and preferred term - age <18 years
Safety population

Primary system organ class Preferred term	RAD001 N=90 n (%)
Cardiac disorders	
- Total	2 (2.2)
Atrioventricular block	1 (1.1)
Extrasystoles	1 (1.1)
Musculoskeletal and connective tissue disorders	
- Total	2 (2.2)
Back pain	1 (1.1)
Muscle spasms	1 (1.1)
Renal and urinary disorders	
- Total	2 (2.2)
Nephrolithiasis	1 (1.1)
Proteinuria	1 (1.1)
Immune system disorders	
- Total	1 (1.1)
Immunodeficiency	1 (1.1)

Table 14.3.1-1.1a (Page 9 of 9)
Number of patients with adverse events, by primary system organ class and preferred term - age <18 years
Safety population

Primary system organ class Preferred term	RAD001 N=90 n (%)
Vascular disorders	
- Total	1 (1.1)
Hypertension	1 (1.1)

Assessor's comment:
The pattern of AEs in the paediatric population (excluding 30 adult patients) is in essence the same as a) in the overall population and b) in table 3 of the current SmPC describing AEs as of the two SEGA trials C2485 and M2301 (including its extension) listing 'Upper respiratory tract infection', 'Hypercholesterolaemia , 'Stomatitis 'Amenorrhoea', 'menstruation irregular' as very common AEs of everolimus in SEGA. The only significant is that metabolism and nutrition disorders as well as

reproduction disorders occurred significantly less frequently in trial MIC02 than actually labelled in the current SmPC.

Serious adverse events

The overall incidence of serious adverse events (SAEs) was 26.7% (32 patients).

The most common SAEs were pyrexia (5 patients) and bronchitis (3 patients). Grade 3 SAEs were reported in 22 patients: hydrocephalus, pyrexia, status epilepticus, stomatitis, viral gastroenteritis, vomiting (2 patients each), abdominal pain, adnexal torsion, gastroenteritis, giardiasis, Haemophilus infection, pneumonitis, sepsis, kidney infection, lung infection, urinary tract infection, irritability, pneumonia, diarrhoea, extrasystoles, nephrolithiasis, neutropenia, subdural hematoma, hypokalaemia, headache, somnolence, pneumothorax, sinusitis, atrioventricular block, bronchitis (1 patient each). Grade 4 SAEs were reported in 2 patients: acute respiratory failure, pneumonia aspiration and near drowning in one patient; gastroenteritis in the second patient.

In the paediatric sub-population (90 patients), the overall incidence of serious adverse events was 27.8% (25 patients). The most common serious adverse events were pyrexia (4 patients, 4.4%) and bronchitis (3 patients, 3.3%).

Deaths

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

Important safety risks

Important safety risks, as defined in the Afinitor/Votubia Risk Management Plan Version 9.0/Version 8.0, were reported in the following patients: aphthous stomatitis (18 patients), severe infections (14 patients), stomatitis (10 patients), mouth ulceration (6 patients), pneumonitis (5 patients), irregular menstruation (4 patients), amenorrhea (3 patients), dyslipidemia, menorrhagia, ovarian cyst (2 patients each), proteinuria, hypophosphatemia, neutropenia, adnexal torsion and dysmenorrhea (1 patient each).

Assessor's comment:
The assessor agrees with the overall assessment of the MAH that the safety results trial MIC02 were consistent with the known safety profile of everolimus in TSC and no new safety concerns or unexpected findings were newly identified.

1.3.3. Discussion on clinical aspects

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

> *"A total of 120 patients were treated in the study, 30 adult patients (25%) and 90 pediatric patients (75%).*
>
> *The study confirms the acceptable safety profile of everolimus in patients < 18 years (pediatric sub-population) and > 18 years old, as shown by the low incidence of serious adverse events, Grade 3 or 4 adverse events and worsening of hematology/biochemistry laboratory values. Reported events were consistent with the known safety profile of everolimus and medically manageable with appropriate medical intervention. Furthermore, few premature discontinuations due to adverse events (6.7%) were reported, no deaths occurred during the*

study or 28-day post treatment follow-up period and no significant changes were reported in vital signs from baseline to end of treatment.

Efficacy evaluation based on the investigator's best overall response showed a partial response for most patients (67.5%).

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

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

The assessor agrees with this overall conclusion. It can be added that study MIC02 shows that the initially recommended starting dose recommended in the SmPC was obviously too low and just has been replaced by a more individualised and higher starting dose in the current SmPC.

2. Additional clarifications requested

Based on the data submitted, the MAH should provide a clarification as to the requirement to update section 4.8 (+/- sec. 5.1) of the SmPC (+/-PIL) of Votubia as part of this procedure in order to bring in line this information with the new clinical data available now from study CSR MIC02 as follows:

1. Since the recommended initial dose in study MIC02 (see table 9.3 above) was lower and less precise than currently recommended in the SmPC (4.5 mg/m^2), the MAH should provide blood level simulations at week 2 under the assumption that patients would have received a starting dose of 4.5 mg/m^2. The MAH should comment on the frequency of required dose adjustments after week 2, following current SmPC recommendation, in an age dependent manner.
2. An OMS comment requested the CHMP to consider the addition of the safety results of study MIC02 under Section 4.8 – Paediatric Population which currently reflects the paediatric experience from the pivotal studies. This would allow informing prescribers about ongoing experience with Everolimus in children, confirming an unchanged and consistent safety profile. The CHMP is of the opinion that the OMS comment is right in the way that the new (safety) data would allow to broaden the safety data base as described in section 4.8 of the current Votubia SmPC (without affecting the content essentially). The MAH is requested to reconsider this suggestion (including also thoughts on changes to sec. 5.1 of the SmPC & PIL), and to make an appropriate proposal for an update of the summary of safety, and changes to the PI within this procedure accordingly.

The timetable is a 30 day response timetable with clock stop.

3. Assessment of responses

Response of the MAH to question 1

Reference is made to the enclosed [PK simulation report], providing PK simulation in typical patients with SEGA in an age dependent manner to attain steady state PK trough levels in the target range based on the current SmPC and on protocol used in Study CRAD001MIC02.

In conclusion, the simulations support the current SmPC. The starting dose recommendation of 4.5 mg/m^2 in the SmPC should result in fewer dose adjustments during titration and thus a shorter length of time to attain steady state trough levels in the target range of 5-15 ng/mL compared to the starting dose used in Study MIC02 protocol.

Assessment of Response to question 1

The MAH has submitted the requested simulations as a separate report.

PK simulations made based on the developed PopPK model taking into account the different dosing regimens, especially the actually recommended starting dose in the current SmPC, are appreciated.

Simulations of 24 different scenarios have been made, for 3 different dosing regimen: dosing with dispersible tablet or with regular tablet according to the SmPC dosing regimen and dosing with regular tablets according to the dosing regimen used in Study MIC02. The patient characteristics were combinations of inducer status (absent and present), and BSA of patient (0.5 m^2, 1.0 m^2, 1.5 m^2 and 2.0 m^2). The BSA values chosen correspond to a toddler, a child, and two sizes of adults. Simulations showed that the current SmPC recommendations improved dosing with respect to attaining target Cmin concentrations. For the simulations reflecting SmPC dosing with dispersible or regular tablets, in 5 of the 8 scenarios target Cmin concentrations were directly achieved with the recommended initial dose. On the contrary, with the dosing regimen of study MIC02, in each of the eight scenarios, a dose adjustment was needed, in one scenario dose had even to be adjusted two times.

Nevertheless, also with the dosing schedule defined in the SmPC, dose adjustments were needed for the group of toddlers, the group of toddlers with additional inducers and for children with additional inducers, because with the currently proposed initial dose resulting Cmin concentrations were below the therapeutic concentration range.

For the two patient groups taking additional inducers, this seems acceptable since dosing of inducers can be different between patients and the influence of different inducers might impact the concentrations differently so this should be managed by individual dose titration via TDM.

On the contrary, it is considered not acceptable that the toddlers in general will need a dose adjustment with the current SmPC initial dose, and thus also an additional blood sample for confirmation of the achieved concentration. Therefore further simulations should be done to find out the optimal initial dose for toddlers to directly attain Cmin concentrations in the therapeutic range.

Issue to be resolved by a type II variation

Response of the MAH to question 2

Novartis appreciates the suggestion to include safety and efficacy claims into the SmPC based on Study MIC02, however would like to respectfully put forward the following points to the attention of the reviewer:

The TSC safety pool currently presented in the Votubia SmPC (derived from the Company Core Data Sheet) includes data from two studies in the TSC-SEGA population (CRAD001C2485 and CRAD001M2301, with cut-off dates of 12-Dec-2012 and 11-Jan-2013 respectively), as well as from one study in the TSC- Renal Angiomyolipoma population (CRAD001M2302), with a cut-off date of 01-May-2013.

An updated Adverse Drug Reactions (ADR) table in section 4.8 of the SmPC will be submitted to the Agency by end of March 2015, along with the submission of the final CSR of Study M2301 (as fulfillment of the Specific Obligation to complete Post-authorization measures for the conditional Marketing Authorisation – Annex II section E). The final data from C2485 and M2301 studies will be integrated into the TSC safety pool, reflecting the long-term follow-up of patients for a median duration of exposure of 67.8 months in Study C2485 and 47.1 months in Study M2301.

The TSC safety pool will be further expanded with the planned integration of final data of study CRAD001M2302. Submission to the Agency along with the final CSR of study CRAD001M2302 will take place by Aug-2015 (as fulfillment of the Conditions or restrictions with regard to the safe and effective use of the medicinal product – Annex II section D).

CRAD001MIC02 is an open-label post-marketing expanded access study. Per protocol, investigators were requested to report grade 1 or 2 adverse events, laboratory or test procedure abnormalities only if/when they caused a study drug dose modification or interruption (study protocol section 7.5; CSR section 9.5.3.2). Patients in MIC02 also had a lower median duration of exposure of study medication compared to the overall safety pool. The median duration of exposure in study MIC02 was 395.5 days; this low median duration of exposure can be explained by the fact that many patients moved out of the study early, switching to commercial drug when available or to local transition plans at study sites. This represents a median exposure 3 times less than the median duration of the TSC patients in the safety pool which is slightly higher than 4 years. These differences contribute to an overall observed ADRs reporting rate being substantially lower compared to those observed previously in the 3 studies currently included in the safety pool (51.7 % in Study MIC02 versus 93.6% in the current safety pool).

For these reasons, Novartis considers study CRAD001MIC02 to be less appropriate than studies C2485, M2301 and M2302 for inclusion into the TSC safety pool which is the basis for the ADR table in the EU SmPC section 4.8. Therefore, Novartis does not propose to make any safety claim related to Study MIC02 in section 4.8.

Consistently, Novartis does not consider suitable to add any efficacy claims related to MIC02 study in section 5.1 of the SmPC. As emphasized by the CHMP in his assessment report, efficacy was a secondary objective and should be considered, as actually determined, as "subjective best response" as judged by the local investigators, whereas the definition of the best overall SEGA response" in the C2485 and M2301 studies was based on three objective criteria measured at each radiological assessment by a central review: the reduction in SEGA volume relative to baseline, the absence of unequivocal worsening of non-target SEGA lesions, the absence of new SEGA lesions (≥ 1 cm in longest diameter), and the absence of new or worsening hydrocephalus.

Assessment of Response to question 2

Both the pharmacovigilance and clinical assessors of the Rapporteur agree that the argument of (shorter) exposure (and the so, or by design, caused lower frequencies of ADRs reporting of) trial MIC02 compared to the current SEGA safety pool (M2302 and C2485) put forward by the MAH is a valid argument for not pooling these data with the current safety pool.

The CHMP would like to add that this assessment per se does not preclude reporting safety data as of trial MIC02 separately in section 4.8 of the SmPC. Since the MAH, however, states clearly that he will not make any safety (and efficacy) claim related to study MIC02 (such as e.g. lowering frequencies in the label of AEs), the CHMP is of the opinion that it is also not needed to indicate in the SmPC that the safety pool in paediatric SEGA is actually larger than the pool used to label AEs in section 4.8.

Issue resolved

4. CHMP's overall conclusion and recommendation

Overall conclusion

Safety and efficacy finding of newly submitted study MIC02 in SEGA patients are fully in accordance with results of study C2485 and M2301 already labelled. The benefit-risk of Votubia remains positive.

However, PK simulations submitted upon additional clarification request indicate that the currently recommended starting dose in toddlers (BSA < 0.5 m^2) could be too low. E.g. a 6 mg/m^2 starting dose [in place of the currently recommended of 4.5 mg/m^2] might be more appropriate to achieve c_{min} in the therapeutic range of 5-15 ng/ml already in the first week of treatment. Thus, with a higher starting dose in toddlers steady state concentrations in the therapeutic range can be achieved faster which in addition would reduce further PK monitoring. The decision to recommend a specific, higher starting dose, however, needs further simulations.

In addition, in children younger than 1 year of age metabolism via cytochromes might still be immature. The MAH should clarify whether a warning informing about the immaturity of CYP3A4 metabolic transformation justifies a warning giving this information – in particular provided that new simulations requested will probably render it necessary to recommend a higher starting dose in toddlers (= patients younger than 3 years of age).

Recommendation

☒ The post-authorisation measure is fulfilled:

A Type II variation is requested from the MAH by 31st of August 2015 to amend the product information as follows:

Simulations should be carried out in order to define an appropriate initial dose for patients below the age of 3 years which will directly lead to trough concentrations in the therapeutic range of 5-15 ng/ml. Subsequently, section 4.2 should be updated according to the newly defined dosing regimen in children below the age of 3 years (or in the age of 1-3 years, see below).

In addition, the MAH should consider the potential immaturity of CYP3A4 in children below the age of 1 year which might lead to lower clearances and longer half-lives of everolimus in this age group. The MAH should summarize and describe all PK data available from patients <1 year and evaluate whether there are indications that in this rare patient population alterations in PK may occur. The MAH should propose a comment on this to be mentioned in the SmPC in section 4.4.