5 September 2024
EMA/442156/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Votubia

International non-proprietary name: Everolimus

Procedure No. EMEA/H/C/002311/II/0089

Note

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

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Steps taken for the assessment	
Description	**Date**
Start of procedure	09 Jul 2024
CHMP Rapporteur Assessment Report	16 Aug 2024
PRAC Rapporteur Assessment Report	16 Aug 2024
PRAC members comments	n/a
CHMP members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
Updated CHMP Rapporteur Assessment Report	n/a
PRAC endorsed relevant sections of the assessment report	03 Sep 2024
Start of written procedure	03 Sep 2024
Opinion	05 Sep 2024

Rapporteur:	Janet Koenig
PRAC Rapporteur:	Martin Huber

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 14 June 2024 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Submission of the final report from study CRAD001M2305 listed as a category 3 study in the RMP. This is an interventional PASS study to monitor the growth and development of paediatric patients previously treated with everolimus in study CRAD001M2301 (EXIST-LT). The RMP version 16.0 has also been submitted.

The requested variation proposed amendments to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

The MAH has submitted the final CSR of the Study CRAD001M2305 (hereafter referred to as Study M2305), a phase IIIb/IV, multi-center, long-term follow-up, PASS designed to monitor the growth and sexual development of paediatric patients who initially enrolled in Study M2301 and who were treated or are being treated with everolimus for TSC-associated SEGA, until they reach Tanner Stage V, or until age 16 for females or age 17 for males, whichever occurs first.

While the long-term safety data from this study overall do not suggest there is a negative impact on growth and sexual development in paediatric patients previously treated with everolimus, no firm conclusions can be drawn due to the very limited number of patients included in the study (n=15).

The reported AEs were consistent with the known safety profile of everolimus in the TSC-SEGA patient population and no new safety concerns or signals were identified during the study.

Based on the results of the M2305 study, no changes to the SmPC were proposed nor considered necessary. Currently no regulatory action is required. However, it is recommended to monitor the effects on growth and sexual development in paediatric patients previously treated with everolimus and report it in the next PSURs.

The MAH submitted also a revised RMP (version 16.0 with data lock point of 31 March 2024), in order to introduce the following significant changes:

- Removal of safety concerns "Male infertility" (TSC setting only) and "Female infertility" (TSC setting only) as recommended by PRAC in the Final Assessment Report for Afinitor/Votubia RMP version 15.0.
- Completion of the additional PV activity, study CRAD001M2305, which was a category 3 study in the RMP.
- Removal of safety concerns “Postnatal developmental toxicity” (TSC setting only), “Long-term safety” (TSC setting only) and “Neurocognitive and sexual development in pediatric patients” (TSC setting only) as study CRAD001M2305 is now completed.
- The RMP is also aligned with new RMP template version 6.4 and updated with exposure data from latest PSURs for Afinitor and Votubia with DLP; 31-Mar-2024.

These changes are acceptable.

In addition, as this study was conducted in paediatric population and reached last patient last visit on 18-Dec-2023, it is agreed that this type II variation may be considered as fulfilling the article 46 requirements from a content and timelines perspective.

The benefit-risk balance of Votubia remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Submission of the final report from study CRAD001M2305 listed as a category 3 study in the RMP. This is an interventional PASS study to monitor the growth and development of paediatric patients previously treated with everolimus in study CRAD001M2301 (EXIST-LT). The RMP version 16.0 has also been submitted.

is recommended for approval.

Amendments to the marketing authorisation

The variation requires amendments to the Risk Management Plan.

4. EPAR changes

The table in "Votubia : EPAR - Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Not applicable

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Everolimus is a rapamycin derivative that inhibits the mTOR pathway by acting on mTORC1. Results from study CRAD001M2301 (hereafter referred to as Study M2301) have shown that a significant proportion of patients with advanced TSC associated SEGA benefited from treatment with the mTOR inhibitor everolimus which led to volume reduction of the SEGA lesions. However, the long-term effects of everolimus on the growth and development of paediatric patients treated for TSC associated SEGA were unknown.

Patients with TSC associated SEGA are typically young children at pre-pubertal age whose physical development and sexual maturation are ongoing. mTOR has been shown to be an important regulator of cell growth and proliferation, and it may regulate physical development and sexual maturation. As many patients treated with everolimus (a mTOR inhibitor) in Study M2301 were young at the time of their exposure to the treatment and experienced prolonged exposure to the treatment in that study, they may present an appropriate study population to assess the long-term effects of everolimus treatment on the growth and development of paediatric patients.

The study CRAD001M2305, a phase IIIb/IV, multi-center, long-term follow-up, PASS evaluated the growth and development of paediatric patients affected by previous or ongoing treatment with everolimus for TSC-associated SEGA. The study included all consenting paediatric patients who at the time of completion of Study M2301 had not achieved Tanner Stage V and were younger than 16 years (for females) or 17 years (for males) and were receiving treatment with everolimus in Study M2301 within 6 months before enrolment into the current Study M2305.

Furthermore, Study CRAD001MIC03 (hereafter referred to as the TOSCA registry) was carried out during a similar time frame as Study M2305. Both adult and paediatric patients were enrolled into this registry (designed to collect data on manifestations, interventions, and outcomes in TSC) although many patients were never exposed to mTOR inhibition either before or during the study. The results from TOSCA registry patients not treated with any mTOR inhibitor (a subset of TOSCA) were considered as reference in Study M2305 CSR.

In addition, an updated RMP (version 16.0) was submitted with the CSR. The changes that have been conducted are detailed in section 8.

6. Clinical Safety aspects

6.1. Methods - analysis of data submitted

Study CRAD001M2305

Title of study: Long-term follow-up study to monitor the growth and development of pediatric patients previously treated with everolimus in study CRAD001M2301 (EXIST-LT)

Study centers: Belgium (1), Russia (1), and USA (4)

Study period:

Study initiation date: 17-Dec-2014 (first patient first visit)

Study completion date: 18-Dec-2023 (last patient last visit)

Study objectives:

Objectives	Endpoints
Primary objective:	
Monitoring growth and development of pediatric patients with TSC-associated SEGA (Tuberous Sclerosis Complex) (Subependymal Giant Cell Astrocytoma) who are taking everolimus or have taken everolimus by annual measurements of height, weight for BMI, and Tanner Stage	Percentage of patients who achieved Tanner Stage V at or before age of 16 (females) or 17 (males). Height/BMI standard deviation score by year since baseline Mean endocrine laboratory values (FSH, LH, and estrogen or testosterone) by age
Secondary objectives:	
Determine timing of developmental milestones: menarche (females), thelarche (females), adrenarche (males), Tanner Stage II-V	Age at start of menses (menarche) – for females Age at onset of breast development (thelarche) – for females Age at pubic hair development (adrenarche) – for males Age at Tanner Stage II-V - all patients
Assess neuropsychological development	TAND Checklist individual responses over time since the enrollment date
*Compare CRAD001M2305 and CRAD001MIC03 on height, BMI and sexual development (using Tanner Stages)	*Indirect comparison between CRAD001M2305 and CRAD001MIC03 will be performed on the following endpoints: Percentage of patients who achieved Tanner Stage V at or before age of 16 (females) or 17 (males). Height/BMI standard deviation score by year since baseline.
Safety as assessed by the NCI Common Toxicity Criteria, version 4.03	Safety will be assessed by the National Cancer Institute's (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03. Notes: Safety assessments will consist of monitoring and recording adverse and serious adverse events. Safety follow-up as per product information

*Indirect comparison was not performed due to limiting sample size.

Study design and methodology:

The study was a phase IIIb/IV, multi-center, long-term follow-up, Post-Authorization Safety Study (PASS) evaluating the growth and development of paediatric patients affected by previous or ongoing treatment with everolimus for TSC-associated SEGA. The study included all consenting pediatric patients through an impartial witness and/or the patient's parent or legal guardian who at the time of completion of Study M2301 had not achieved Tanner Stage V and were younger than 16 years (for females) or 17 years (for males) and were receiving treatment with everolimus in Study M2301 within 6 months before enrollment into the current Study M2305.

All the paediatric patients enrolled into the current study had been treated with everolimus in the parent study M2301. However, no current administration of everolimus was required in Study M2305. The paediatric patients could be treated with commercial everolimus in Study M2305 at principal investigator's discretion.

Paediatric patients visited site every 3 months for the collection of AEs, any SAEs, date of menarche (females) and annually for measurement of growth (height, weight), development (Tanner staging, age at thelarche, age at menarche for females, age at adrenarche for males), and pregnancy testing. Endocrine and TAND (TSC-Associated-Neuropsychiatric-Disorders) data were also collected at the patient annual visits. The first study visit took place 3 months after enrollment in Study M2305 and the first annual visit one year after enrollment in Study M2305.

Number of patients (planned and analysed):

It was anticipated that maximum of 50 patients who had participated in Study M2301 would be eligible to enter Study M2305, if they consent to participate.

However, only 15 patients were enrolled into this study, due to delays in study start-up at the country level, resulting in the majority of anticipated patients becoming ineligible to enter the study.

Inclusion and exclusion criteria

Inclusion criteria

1. Paediatric female patients who were on study treatment in Study M2301 within the past 6 months and had not reached Tanner Stage V and were younger than age 16 at the time of completion of Study M2301 or

2. Paediatric male patients who were on study treatment in Study M2301 within the past 6 months and had not reached Tanner Stage V and were younger than age 17 at the time of completion of Study M2301.

3. Written informed consent according to local guidelines.

Exclusion criteria

1. Paediatric female patients who were on study treatment in Study M2301 and have not reached Tanner Stage V but are within 3 months of turning age 16 or

2. Paediatric male patients who were on study treatment in Study M2301 and have not reached Tanner Stage V but are within 3 months of turning age 17.

3. Any patient who was pregnant prior to start of Study M2305 [Study M2305 Section 9.3]

Test and reference therapies

Not applicable, as the participation in this study did not require the administration of everolimus by the sponsor (patients may have received commercial everolimus). At the discretion of the investigator, paediatric patients were treated with commercially available everolimus, as per local product information / standard of care. No reference therapy was administered.

Protocol amendments:

The study protocol was amended once in order to address comments received from the CHMP. The Amended Protocol Version 01 is dated 11-Aug-2014.

Statistical methods:

No hypothesis testing was done. Following analyses sets were used:

The Full Analysis Set (FAS): For study M2305, FAS consisted of all patients enrolled in this study. For TOSCA registry, FAS consisted of all patients enrolled in the TOSCA registry whose age at study entry was below 16 (for female) and 17 (for male) years and who never received an mTOR inhibitor throughout the registry follow-up period nor recorded as prior or ongoing treatment at the baseline visit.

The Full Analysis Set for sexual development (FAS Puberty): For Study M2305, FAS Puberty consisted of the FAS patients defined above. For TOSCA registry, FAS Puberty consisted of the FAS patients defined above but restricting from the patients to those aged between 9 to 17 years (for, females 9 to 16 years, males 9 to 17 years) at registry entry. The TOSCA registry was designed to collect Tanner Staging until 2017 (i.e. 4 to 6 years of follow-up). Thus, it is considered adequate to select only TOSCA

patients aged between 9 to 17 years old at the time of entry to the registry to allow for obtaining puberty data corresponding to the peri-pubertal time frame.

The Safety Set included all paediatric patients enrolled in this follow-up Study M2305 who had at least one-post baseline safety assessment.

The indirect comparison between the Study M2305 and TOSCA registry was planned but was not performed considering the unlikelihood of making a robust analysis with the limited enrolment into Study M2305. Only descriptive summary for each study were provided.

6.2. Results

Table 1: Analysis sets by study

Analysis set	CRAD001M2305 (N=15) n (%)	TOSCA (N=1264) n (%)
Full analysis set	15(100)	1264(100)
Full analysis set Puberty	15(100)	380(30.1)
Safety set	14(93.3)	N/A

FAS of CRAD001M2305, consists of all patients enrolled in this study.

TOSCA-FAS consists of all patients enrolled in the registry who are below 16 years (females) and 17 years (males) at study entry and never received any mTOR inhibitor throughout the study.

FAS puberty of CRAD001M2305, same as FAS.

TOSCA-FAS Puberty consists of FAS patients but restricting to age between 9 - 16 years (females) and 9 - 17 years (males) at registry entry.

Safety set is only defined for CRAD001M2305 study and includes all patients enrolled who have at least one-post baseline assessment and have been exposed to everolimus in the parent study CRAD001M2301.

One patient who was excluded from the safety set fulfilled eligibility criteria but discontinued at baseline without any safety follow-up.

Patient disposition

Table 2: Patient disposition in Study M2305 (FAS)

Disposition Reason	CRAD001M2305 N=15 n (%)
Patients Treated with everolimus	15 (100)
Discontinued Treatment	6 (40.0)
Primary reason for discontinuation of everolimus	
Death	1 (6.7)
Disease progression	1 (6.7)
Physician's decision	4 (26.7)
Discontinued Study	2 (13.3)
Primary reason for patients to discontinue Study	
Death	1 (6.7)
Physician's decision	1 (6.7)

Data from study M2305 is presented.
One patient has missing information of end of study visit, hence not included in the study discontinuation analysis.

Participant exposure (Safety Set)

Table 3: Duration of exposure to everolimus in Study M2305 (Safety set)

Total duration of exposure categories	**CRAD001M2305 N=14**
Duration of Exposure (years) at CRAD001M2305	
n	14
Mean (SD)	4.492 (2.5747)
Median	4.930
Q1 - Q3	1.333 - 6.223
Min – Max	0.81 - 9.03
Total Duration of Exposure (years)	
Total duration of exposure categories	**CRAD001M2305 N=14**
n	14
Mean (SD)	8.161 (2.3055)
Median	8.604
Q1 - Q3	5.947 - 9.536
Min – Max	4.04 - 12.01
Total Duration of Exposure categories (years) -n (%)	
< 5	1 (7.1)
5 - < 10	10 (71.4)
≥ 10	3 (21.4)

For 'Duration of Exposure in CRAD001M2305' only exposure during the period of study M2305 is presented.
For 'Total duration of exposure' pooled data from both studies M2301 and M2305 is presented. A patient is counted only once in the category.

Primary endpoints:

Growth and sexual development

Table 4: Percentage of patients who achieved Tanner stage V by study (FAS puberty) (Male)

Gender: Male	**CRAD001M2305 N=7**	**TOSCA N=200**
Number of patients with Puberty data*	7	50
Patients at Tanner stage V at baseline^	0	12
Patients not achieved Tanner Stage V at baseline*	7	38

Tanner Stage V at the end of study		
Reached Tanner stage V – by age 17 – n (%)	6 (85.7)	4 (10.5)
Not yet reached Tanner stage V by age 17 – n (%)	0	1 (2.6)
Discontinued before age 17 without reaching Tanner stage V – n (%)	1 (14.3)	33 (86.8)
95% CI for Tanner Stage V attainment rate by age 17 [1]	[42.1, 99.6]	[2.9, 24.8]

For CRAD001M2305, pooled data from both studies M2301 and M2305 is presented.
In Study M2305, FAS puberty consisted of 7 male patients.
TOSCA-FAS puberty consisted of 200 male patients.
*Percentage calculation is based on the patients not achieved Tanner stage V at baseline .
[1] Exact 95% confidence interval obtained from the Clopper-Pearson method.

Table 5: Percentage of patients who achieved Tanner stage V by study (FAS puberty) (Female)

Gender: Female	**CRAD001M2305 N=8**	**TOSCA N=180**
Number of patients with Puberty data*	**8**	**45**
Patients at Tanner stage V at baseline^	**0**	**11**
Patients not achieved Tanner stage V at baseline	**8**	**34**
Tanner Stage V data at the end of study		
Reached Tanner stage V by age 16 – n (%)	4 (50.0)	5 (14.7)
Not yet reached Tanner stage V by age 16 – n (%)	0	9 (26.5)
Discontinued before age 16 without reaching Tanner stage V – n(%)	4 (50.0)	20 (58.8)
95% CI for Tanner Stage V attainment rate by age 16 [1]	[15.7, 84.3]	[5.0, 31.1]

For CRAD001M2305, pooled data from both studies M2301 and M2305 is presented. In Study M2305, FAS puberty consisted of 8 female patients.
TOSCA-FAS puberty consisted of 180 female patients.
* Percentage calculation is based on the 'Patients not achieved Tanner stage V at baseline'.
^For the TOSCA patients, the baseline value is taken from the first available assessment on or after the enrollment date.

[1] Exact 95% confidence interval obtained from the Clopper-Pearson method.

Height and BMI

Table 6: Growth data by time window of study (FAS)

CRAD001M2305 (N=15) Age category: ≤ 12 Years

		Baseline	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Height SDS	n	15	15	14	15	15	12
	Notably low - n (%)	2 (13.3)	1 (6.7)	2 (14.3)	2 (13.3)	2 (13.3)	2 (16.7)
	Notably high - n (%)	1 (6.7)	0	0	0	1 (6.7)	0
BMI SDS	n	15	15	14	15	15	12
	Notably low - n (%)	0	0	1 (7.1)	0	0	1 (8.3)

	Notably high - n (%)	4 (26.7)	1 (6.7)	1 (7.1)	2 (13.3)	1 (6.7)	1 (8.3)
	Baseline		**Year 6**	**Year 7**	**Year 8**	**Year 9**	**Year 10**
Height SDS	n		12	9	9	8	3
	Notably low - n (%)		1 (8.3)	1 (11.1)	0	0	0
	Notably high - n (%)		1 (8.3)	1 (11.1)	1 (11.1)	0	0
BMI SDS	n		12	9	9	8	3
	Notably low - n (%)		2 (16.7)	0	1 (11.1)	2 (25.0)	1 (33.3)
	Notably high - n (%)		1 (8.3)	2 (22.2)	2 (22.2)	1 (12.5)	1 (33.3)

TOSCA (N=1004) Age category: ≤ 12 Years

		Baseline	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Height SDS	n	598	664	608	482	165	3
	Notably low - n (%)	51 (8.5)	52 (7.8)	44 (7.2)	29 (6.0)	5 (3.0)	0
	Notably high - n (%)	78 (13.0)	99 (14.9)	95 (15.6)	64 (13.3)	17 (10.3)	0
BMI SDS	n	598	664	606	478	165	3
	Notably low - n (%)	29 (4.8)	28 (4.2)	32 (5.3)	24 (5.0)	5 (3.0)	0
	Notably high - n (%)	147 (24.6)	141 (21.2)	135 (22.3)	102 (21.3)	33 (20.0)	1 (33.3)

For CRAD001M2305, pooled data from both studies M2301 and M2305 is presented. In Study M2305, FAS consisted of 15 patients.
TOSCA FAS consisted of 1264 patients, with (N=1004) in age category: ≤ 12 Years.
For Study M2305 – baseline was the last available assessment on or before the start of everolimus in the parent study M2301. Baseline in TOSCA was first available assessment in TOSCA. Percentages are calculated based on "n".

Endocrine Parameters

Table 7: Endocrines values by study by gender and age (FAS) (Male)

Gender: Male	Statistics	LH (U/L)		FSH (U/L)		Testosterone (nmol/L)	
Age		M2305 (N=7)	TOSCA (N=675)	M2305 (N=7)	TOSCA (N=675)	M2305 (N=7)	TOSCA (N=675)
Test at 10-year age	n	4	0	4	1	4	1
	Mean (SD)	1.0 (1.47)		1.5 (1.34)	1.3 (NA)	0.7 (1.17)	1.4 (NA)
Test at 11-year age	n	6		6		6	
	Mean (SD)	1.0 (0.77)		1.7 (1.11)		2.5 (4.60)	
Test at 12-year age	n	7	1	7	1	7	1
	Mean (SD)	1.8 (1.22)	5.5 (NA)	2.1 (0.67)	1.6 (NA)	3.8 (4.29)	4861.0 (NA)
Test at 13-year age	n	6		6		6	
	Mean (SD)	2.4 (2.26)		2.9 (1.81)		4.3 (4.04)	
Test at 14-year age	n	6		6		6	
	Mean (SD)	2.9 (2.18)		4.6 (4.29)		7.2 (4.34)	
Test at 15-year age	n	4		4		4	
	Mean (SD)	2.5 (1.07)		3.3 (0.61)		12.9 (6.28)	
Test at 16-year age	n	3	1	3	0	3	1
	Mean (SD)	3.5 (0.32)	0.9 (NA)	6.0 (3.01)		15.5 (3.93)	2.2 (NA)

For CRAD001M2305, pooled data from both studies M2301 and M2305 is presented. NA – Not applicable
In Study M2305, FAS consisted of 7 male patients. TOSCA-FAS consisted of 675 male patients.
In Study M2305, blood samples collected annually (starting at age 10 until end of study participation) for assessment of endocrine levels were analysed at local laboratories.

Table 8: Endocrines values by study by gender and age (FAS) (Female)

Gender: Female	Statistics	LH (U/L)		FSH (U/L)		Estrogen (ng/L)	
Age		M2305 (N=8)	TOSCA (N=589)	M2305 (N=8)	TOSCA (N=589)	M2305 (N=8)	TOSCA (N=589)
Test at 10-year age	n	2		2		1	
	Mean (SD)	5.1 (3.89)		3.4 (2.68)		139.8 (NA)	
Test at 11-year age	n	7		7		4	
	Mean (SD)	3.2 (2.47)		3.5 (1.61)		80.5 (119.22)	
Test at 12-year age	n	7		7		3	
	Mean (SD)	7.8 (6.73)		5.6 (2.43)		43.7 (41.26)	
Test at 13-year age	n	5	1	5	0	2	0
	Mean (SD)	4.4 (3.08)	2.4 (NA)	5.0 (0.80)		50.0 (7.07)	
Test at 14-year age	n	6		6		2	
	Mean (SD)	5.3 (6.97)		2.6 (2.05)		139.0 (141.42)	
Test at 15-year age	n	4		4		4	
	Mean (SD)	7.5 (10.96)		2.5 (2.28)		47.7 (48.89)	
Test at 16-year age	n	4	1	4	1	4	0
	Mean (SD)	3.7 (2.69)	12.2	2.8 (2.05)	3.8	149.7 (128.21)	

For CRAD001M2305, pooled data from both studies M2301 and M2305 is presented. NA – Not applicable
In Study M2305, FAS consisted of 8 female patients. TOSCA-FAS consisted of 589 female patients.
In Study M2305, blood samples collected annually (starting at age 10 until end of study participation) for assessment of endocrine levels were analysed at local laboratories.

Secondary endpoints:

Menarche and thelarche in females

Table 9: Puberty stage - Age at Menarche - Females patients (Safety Set)

Age at Menarche	CRAD001M2305 N=7
Number of patients without menarche prior to start of everolimus in the parent study CRAD001M2301	7
Menarche attained	7 (100.0)
Censored	0
Kaplan-Meier estimates [95% CI] of age at menarche:	
25th percentile	11.5 (11.0, 12.5)
Median	12.5 (11.0, 13.6)
75th percentile	13.6 (12.2, NE)
Kaplan-Meier estimates - proportions [95% CI] for attaining menarche at:	
Age 10	0.0 (0.0, 0.0)
Age 11	14.3 (2.1, 66.6)
Age 12	28.6 (8.0, 74.2)
Age 13	57.1 (26.6, 90.2)
Age 14	85.7 (53.5, 99.3)
Age 15	85.7 (53.5, 99.3)

For CRAD001M2305, pooled data from both studies M2301 and M2305 is presented.
Two patients attained Menarche while in study M2301 and before enrollment into study M2305. For Study M2305 – baseline was the last available assessment on or before the start of everolimus in the parent study M2301.
NE – Not evaluable

Table 10: Puberty stage - Age at Thelarche - Females patients (Safety Set)

Age at Thelarche	CRAD001M2305 N=7

Number of patients without thelarche prior to start of everolimus in the parent study CRAD001M2301	5
Thelarche attained	5 (100.0)
Censored	0
Kaplan-Meier estimates [95% CI] of age at thelarche:	
25th percentile	10.1 (9.1, 11.0)
Median	10.2 (9.1, NE)
75th percentile	11.0 (9.1, NE)
Kaplan-Meier estimates - proportions [95% CI] for attaining thelarche at:	
Age 10	20.0 (3.1, 79.6)
Age 11	80.0 (41.8, 99.2)
Age 12	NE

For CRAD001M2305, pooled data from both studies M2301 and M2305 is presented.
For Study M2305 – baseline was the last available assessment on or before the start of everolimus in the parent study M2301.

NE – Not evaluable

Adrenarche in males

Table 11 Puberty stage - Age at Adrenarche - Males patients (Safety Set)

Age at Adrenarche	**CRAD001M2305 N=7**
Number of patients without adrenarche prior to start of everolimus in the parent study CRAD001M2301	7
Adrenarche attained	7 (100.0)
Censored	0
Kaplan-Meier estimates [95% CI] of age at adrenarche:	
25th percentile	10.0 (10.0, 11.0)
Median	11.0 (10.0, 11.6)
75th percentile	11.6 (10.5, NE)
Kaplan-Meier estimates - proportions [95% CI] for attaining adrenarche at:	
Age 10	28.6 (8.0, 74.2)
Age 11	57.1 (26.6, 90.2)
Age 12	85.7 (53.5, 99.3)
Age 13	85.7 (53.5, 99.3)
Age 14	NE

For CRAD001M2305, pooled data from both studies M2301 and M2305 is presented.
For Study M2305 – baseline was the last available assessment on or before the start of everolimus in the parent study M2301.

NE – Not evaluable

Age at Tanner Stage II-V

Table 12 Puberty stage - Age at Tanner Stages II to V (FAS Puberty) (Male)

	CRAD001M2305 N=7	**TOSCA N=200**

Gender: Male	Pubic hair	Genitalia	Pubic hair	Genitalia
Patients with Tanner Stage 1 at baseline [1]	6	6	19	18
Tanner Stage 2 attained	6 (100)	6 (100)	9 (47.4)	7 (38.9)
Median [95% CI] of age at Tanner Stage 2	11.8 (10.2, NE)	11.9 (10.4, NE)	14.3 (13.7,15.4)	14.3 (13.7, NE)
Patients with Tanner Stage ≤2 at baseline [1]	7	7	31	30
Tanner Stage 3 attained	6 (85.7)	6 (85.7)	14 (45.2)	13 (43.3)
Median [95% CI] of age at Tanner Stage 3	13.3 (11.3, NE)	12.6 (11.3,14.2)	14.3 (13.8,15.5)	14.3 (13.8,15.5)
Patients with Tanner Stage ≤3 at baseline [1]	7	7	38	37
Tanner Stage 4 attained	6 (85.7)	6 (85.7)	9 (23.7)	7 (18.9)
Median [95% CI] of age at Tanner Stage 4	14.2 (11.3, NE)	14.2 (11.3, NE)	19.3 (14.9, NE)	19.3 (14.9, NE)
Patients with Tanner Stage ≤4 at baseline [1]	7	7	50	49
Tanner Stage 5 attained	5 (71.4)	6 (85.7)	6 (12.0)	7 (14.3)
Median [95% CI] of age at Tanner Stage 5	16.4 (15.3, NE)	16.4 (12.7, NE)	18.6 (16.1, NE)	18.6 (16.1, NE)

For CRAD001M2305, pooled data from both studies M2301 and M2305 is presented.

[1] For the CRAD001M2305 patients, Tanner Stage evaluation was not necessarily collected at baseline in the parent study CRAD001M2301, so if assessment prior to start of everolimus is not available, the first assessment on everolimus is considered as baseline.

For TOSCA, baseline is defined as the first available assessment after enrollment date. NE – not evaluable.

In Study M2305, FAS puberty consisted of 7 male patients.

TOSCA-FAS puberty consisted of 200 male patients.

Table 13 Puberty stage - Age at Tanner Stages II to V (FAS Puberty) (Female)

	CRAD001M2305 N=8		TOSCA N=180	
Gender: Female	**Pubic hair**	**Breast development**	**Pubic hair**	**Breast development**
Patients with Tanner Stage 1 at baseline [1]	8	7	11	10
Tanner Stage 2 attained	8 (100)	7 (100)	8 (72.7)	7 (70.0)
Median [95% CI] of age at Tanner Stage 2	10.4 (7.3,11.8)	11.5 (9.9,11.8)	14.3 (12.1,17.0)	12.6 (12.1,14.5)
Patients with Tanner Stage ≤2 at baseline [1]	8	8	19	22
Tanner Stage 3 attained	8 (100)	7 (87.5)	12 (63.2)	13 (59.1)
Median [95% CI] of age at Tanner Stage 3	12.2 (10.4,12.8)	12.5 (10.4,14.6)	14.3 (13.1,15.7)	15.4 (13.2,17.0)
Patients with Tanner Stage ≤3 at baseline [1]	8	8	33	35
Tanner Stage 4 attained	6 (75.0)	7 (87.5)	12 (36.4)	14 (40.0)
Median [95% CI] of age at Tanner Stage 4	13.4 (11.6,14.5)	13.8 (12.7,14.6)	16.0 (15.2,18.0)	16.0 (15.2,17.8)
Patients with Tanner Stage ≤4 at baseline [1]	8	8	44	45
Tanner Stage 5 attained	4 (50.0)	2 (25.0)	7 (15.9)	6 (13.3)
Median [95% CI] of age at Tanner Stage 5	16.0 (13.8, NE)	NE (13.8, NE)	17.5 (16.8, NE)	18.4 (16.8, NE)

Assessment of neuropsychological development – TAND checklist

A higher percentage of neuropsychological disorders were observed in Study M2305 compared to TOSCA (behavioral disorders, psychiatric disorders, scholastic issues, difficulty in specific brain skills, psychological issues, physical dependency, and intellectual disability). However, this may be due to small number of patients included in the analyses and the small number of positive cases. The absolute difference in positive cases (baseline vs post-baseline) in Study M2305 was in 1 to 3 patients. Only result from the Study M2305 are included below:

Basic development milestones

In the Study M2305, overall, all 15 (100%) patients achieved basic developmental milestones of first smiled, sat without support, and used single words. All except 1 (93.3%) patient achieved the following basic developmental milestones: walked without holding on, used two words, was toilet trained during the day and night.

Behavioural disorders

The number of patients who newly developed behavioral disorders during the study was low, with an absolute difference of 1 to 3 patients between baseline and post-baseline data for majority of the disorders.

Psychiatric disorders

• From baseline to overall, patients with autism spectrum disorder increased from 4 (26.7%) patients to 7 (46.7%) patients.

• Attention deficit hyperactivity disorder (ADHD) in 5 (33.3%) patients at baseline had increased to 9 (60.0%) patients overall.

• Anxiety disorder at baseline was observed in 4 (26.7%) patients and overall increased to 7 (46.7%) patients.

• None of the patients reported a psychotic disorder, including schizophrenia

Scholastic issues

• Twelve (80.0%) patients at baseline had scholastic issues (reading, writing, spelling, and mathematics) and overall, 14 (93.3%) of patients experienced scholastic issues.

Specific brain skills

Difficulty in memory was observed in 7 (46.7%) patients at baseline and overall, in 12 (80.0%) patients.

• Difficulty in attention and dual-tasking skills were each observed in 12 (80.0%) patients at baseline and overall, in 14 (93.3%) patients.

• Difficulty in visuo-spatial tasks were observed in 8 (53.3%) patients at baseline and overall, in 13 (86.7%) patients.

• Difficulty in executive skills were observed in 10 (66.7%) patients at baseline and overall, in all 15 (100%) patients.

• Getting disoriented was observed in 7 (46.7%) patients at baseline and overall, in 12 (80.0%) patients

Psychological issues

• Low self-esteem was observed in 2 (13.3%) patients at baseline and overall, in 6 (40.0%) patients.

• Very high level of stress in families was observed in 6 (40.0%) patients at baseline and overall, in 8 (53.3%) patients.

• Very high levels of stress between parents were observed in 5 (33.3%) patients at baseline and overall, in 7 (46.7%) patients

Language skills

• Of the 2 (13.3%) patients who were non-verbal at baseline, both remained non-verbal at post-baseline.

• Of the 7 (46.7%) patients who had simple language at baseline, 6 (40.0%) patients remained with simple language at post-baseline and information on language skills was missing in 1 (6.7%) patient.

• Of the 6 (40.0%) patients who were fluent at baseline, 4 remained fluent at post-baseline and information on language skills was missing in 2 (13.3%) patients.

Physical dependency

• Of the 8 (53.3%) patients who had some self-care skills at baseline, 5 (33.3%) remained with some self-care skills and 1 (6.7%) patient was dependent on others at post-baseline. The information on physical dependency was missing in 2 (13.3%) patients.

• Of the 4 (26.7%) patients who were completely independent at baseline, 1 (6.7%) remained independent and 2 (13.3%) patients had some self-care skills at post-baseline. The information on physical dependency was missing in 1 (6.7%) patient.

Intelligence quotient

• Of the 3 (20.0%) patients who had a normal IQ at baseline, 1 (6.7%) patient had a normal IQ, 1(6.7%) patient had borderline IQ at post-baseline. The information on IQ was missing in 1 (6.7%) patient.

• The 1 (6.7%) patient who had a borderline IQ at baseline, remained with borderline IQ at post-baseline.

• Of the 4 (26.7%) patients with mild IQ disability at baseline, 1 (6.7%) patient had mild IQ disability, and 1 (6.7%) patient had moderate IQ disability at post-baseline. The information on IQ was missing in 2 (13.3%) patients.

• Of the 3 (20.0%) patients with moderate IQ disability at baseline, remained with moderate IQ disability at post-baseline.

• Of the 2 (13.3%) patients with severe IQ disability at baseline, 1 (6.7%) patient had moderate IQ disability and 1 (6.7%) patient had profound IQ disability at post-baseline.

• Of the 2 (13.3%) patients with missing information on IQ at baseline, 1 (6.7%) patient had normal IQ at post-baseline and the information on IQ remained missing in 1 (6.7%) patient.

Intellectual ability

• Of the 3 (20.0%) patients with normal intellectual ability at baseline, 1 (6.7%) was with normal, 1 (6.7%) was in mild-moderate intellectual disability at post-baseline. The information on intellectual ability was missing in 1 (6.7%) patient.

• Of the 6 (40.0%) patients in mild-moderate intellectual disability at baseline, 5 (33.3%) remained in mild-moderate intellectual disability at post-baseline. The information on intellectual ability was missing in 1 (6.7%) patient.

• Of the 5 (33.3%) patients in severe-profound intellectual disability at baseline, 3 (20.0%) remained in severe-profound, 1 (6.7%) was in mild-moderate intellectual disability at post-baseline. The information on intellectual ability was missing in 1 (6.7%) patient.

• Of the 1 (6.7%) patient with missing information on intellectual ability at baseline, was in mild-moderate intellectual disability at post-baseline.

Adverse events

Table 14: Overview of adverse events in Study M2305 (Safety Set)

	CRAD001M2305 N=14	
Category	**All grades n (%)**	**Grade 3/4 n (%)**
Adverse events	12 (85.7)	6 (42.9)
Treatment-related	6 (42.9)	1 (7.1)
SAEs	6 (42.9)	6 (42.9)
Treatment-related	1 (7.1)	1 (7.1)
Fatal SAEs	1 (7.1)	1 (7.1)
Treatment-related	0	0
AEs leading to treatment discontinuation	0	0
AEs leading to dose adjustment	6 (42.9)	3 (21.4)

Treatment-related	2 (14.3)	1 (7.1)

Data from study M2305 is presented. Treatment emergent AEs are summarized.
A patient with multiple occurrences of an AE is counted only once in the AE category.
A patient with multiple adverse events within a grouping is counted only once in the total row.
MedDRA version 26.1 and CTC version 4.03.

Common adverse events

Table 15 Adverse events regardless of study drug relationship by preferred term (reported in at least 2 patients) and maximum grade in Study M2305 (Safety set)

	CRAD001M2305 N=14	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**
Number of patients with at least one event	**12 (85.7)**	**6 (42.9)**
Pyrexia	6 (42.9)	2 (14.3)
Ear infection	4 (28.6)	0
Nasopharyngitis	4 (28.6)	0
Pneumonia	4 (28.6)	2 (14.3)
Seizure	4 (28.6)	3 (21.4)
Anaemia	3 (21.4)	0
Anxiety	3 (21.4)	0
Diarrhoea	3 (21.4)	0
Eczema	3 (21.4)	0
Headache	3 (21.4)	0
Seasonal allergy	3 (21.4)	0
Sinusitis	3 (21.4)	0
Stomatitis	3 (21.4)	0
Upper respiratory tract infection	3 (21.4)	0
Abdominal pain upper	2 (14.3)	0
Attention deficit hyperactivity disorder	2 (14.3)	0
Constipation	2 (14.3)	0
Cough	2 (14.3)	0
Influenza	2 (14.3)	0
Mouth ulceration	2 (14.3)	0
Otitis media	2 (14.3)	0
Pharyngitis streptococcal	2 (14.3)	0

Data from study M2305 is presented.
Treatment emergent AEs are summarized.
A patient with multiple occurrences of the same AE is counted only once in the AE category.
A patient with multiple grades for different occurrences of the same AE is only counted under the maximum grade.
MedDRA version 26.1 and CTC version 4.03.

Table 16 Adverse events suspected to be related to study drug by preferred term and maximum grade in Study M2305 (Safety Set)

	CRAD001M2305 N=14	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**
Number of patients with at least one event	6 (42.9)	1 (7.1)
Stomatitis	3 (21.4)	0
Abdominal pain upper	1 (7.1)	0
Diarrhoea	1 (7.1)	0
Mouth ulceration	1 (7.1)	0
Oral pain	1 (7.1)	0
Pyrexia	1 (7.1)	1 (7.1)
Croup infectious	1 (7.1)	0
Nasopharyngitis	1 (7.1)	0
Otitis media	1 (7.1)	0
Pharyngitis streptococcal	1 (7.1)	0
Pneumonia	1 (7.1)	1 (7.1)
Upper respiratory tract infection	1 (7.1)	0

Data from study M2305 is presented.
Treatment emergent AEs are summarized.
A patient with multiple occurrences of an AE is counted only once in the AE category.
A patient with multiple grades for an AE while on a treatment, is only counted under the maximum grade.
MedDRA version 26.1 and CTC version 4.03.

Serious adverse events

Table 17 Serious adverse events, regardless of study drug relationship by preferred term and maximum grade in Study M2305 (Safety Set)

	CRAD001M2305 N=14	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**
Number of patients with at least one event	6 (42.9)	6 (42.9)
Pyrexia	2 (14.3)	1 (7.1)
Drowning	1 (7.1)	1 (7.1)
Pneumonia	2 (14.3)	2 (14.3)
Arthritis infective	1 (7.1)	1 (7.1)
Influenza	1 (7.1)	0
Staphylococcal infection	1 (7.1)	1 (7.1)
Near drowning	1 (7.1)	1 (7.1)
Post procedural complication	1 (7.1)	1 (7.1)
Astrocytoma, low grade	1 (7.1)	1 (7.1)
Seizure	2 (14.3)	2 (14.3)
Status epilepticus	1 (7.1)	1 (7.1)

Data from study M2305 is presented.

Treatment emergent AEs are summarized.
A patient with multiple occurrences of an AE is counted only once in the AE category.
A patient with multiple grades for an AE while on a treatment, is only counted under the maximum grade.

MedDRA version 26.1 and CTC version 4.03

Adverse events of special interest

The following topics were considered as AESI based on the safety profile of everolimus: muscle wasting / muscle loss, postnatal developmental toxicity, male infertility, hemorrhages and female infertility.

Of these AESI, only hemorrhage (3 patients, 21.4%) was reported in this study. Three patients reported 4 AESIs of hemorrhage: hypofibrinogenemia, menorrhagia, heavy menstrual bleeding and contusion. None of the hemorrhage events were suspected to be treatment related. One patient had grade 3 hypofibrinogenemia, and the other 3 events were grade 2 or lower in severity.

6.3. Discussion

The MAH has submitted the final CSR of the Study M2305, a phase IIIb/IV, multi-center, long-term follow-up, PASS evaluating the growth and development of paediatric patients affected by previous or ongoing treatment with everolimus for TSC-associated SEGA.

Due to delay in study start-up and the fact that the majority of the anticipated patients (up to 50) rendered ineligible to enter the study, only 15 paediatric patients from the parent Study M2301 were enrolled into Study M2305.

The median duration of exposure to everolimus during the period of Study M2305 was 4.93 years (range: 0.81 - 9.03). The median duration of cumulative exposure to everolimus (during Study M2301 and Study M2305) was 8.60 years (range: 4.04 - 12.01). Ten (71.4%) patients had 5 to <10 years of cumulative exposure to everolimus and 3 patients (21.4%) had ≥ 10 years of cumulative exposure.

The majority of patients (13, 86.7%) completed the study as per protocol. 6 patients discontinued the treatment. The reasons for discontinuation included death (1 patient, 6.7%), disease progression (1 patient, 6.7%) and physician's decision (4 patients, 26.7%). Two patients discontinued the study due to physician's decision (1 patient, 6.7%), and death (1 patient, 6.7%), respectively.

Growth and sexual development

Five patients discontinued the study before reaching Tanner Stage 5. All the other patients who continued their participation until the end of study reached Tanner Stage 5 during the study. By age 17 years, 6 (85.7%) male patients and by age 16 years, 4 (50.0%) female patients reached Tanner Stage V.

The number of patients with notably low or high SDS of height or BMI overall did not increase over time after start of everolimus. By year 5, two patients had notably low height SDS and none with notably high height SDS. By year 10, events of notably low or notably high height SDS were not observed. By year 5 and year 10, notably low and high BMI SDS were observed in one patient each. However limited data was available by year 10 (N=3).

Endocrine values were reported only in 3 male and 4 female patients. The mean (SD) endocrine laboratory values at 16 years of age in 3 male patients were: LH: 3.5 U/L (0.32), FSH: 6.0 U/L (3.01),

testosterone: 15.5 nmol/L (3.93) and in 4 female patients: LH: 3.7 U/L (2.69), FSH: 2.8 U/L (2.05) and estrogen: 149.7 ng/L (128.21).

Due to the inconsistencies of laboratory assessments across Study M2301 and Study M2305 (central vs local laboratory), also due to the missing data for the majority of patients, the mean endocrine values may not be meaningful. As TOSCA was an observational registry and did not mandate endocrine laboratory tests, only limited data was available for these parameters.

All the 7 female patients without menarche prior to start of everolimus in the parent Study M2301, attained menarche during the treatment with everolimus. Two patients attained menarche after completion of Study M2301 and prior to participating in Study M2305. All the 5 patients without menarche at baseline of Study M2305 attained menarche during Study M2305, and the median age at menarche was 12.5 years (95% CI: 11.0; 13.6).

All the 5 female patients without thelarche prior to start of everolimus in the parent Study M2301, had attained thelarche during Study M2305, and the median age at thelarche was 10.2 years (95% CI: 9.1; NE).

All the 7 male patients without adrenarche prior to start of everolimus in the parent Study M2301, had attained adrenarche during the Study M2305, and the median age at adrenarche was 11.0 years (95% CI: 10.0; 11.6).

In the assessment of the neuropsychological development there was no clear trend in any of the TAND checklist parameters: Basic developmental milestones, neuropsychiatric disorders and features, physical dependency, and intelligence quotient.

Although one of the objectives was to compare Study M2305 and TOSCA registry with regards to the height, BMI and sexual development (using Tanner Stages) to enable the interpretation of Study M2305 results and to differentiate the impact of the TSC condition versus any potential impact of everolimus on growth and sexual development, this indirect comparison between the two studies was not performed due to limiting sample size in Study M2305, and limited data available in TOSCA.

Adverse events

AEs were reported in 12 (85.7%) patients. Overall, the AEs that occurred in >1 patient were pyrexia (6 patients, 42.9%), ear infection, nasopharyngitis, pneumonia and seizure (each in 4 patients, 28.6%), anaemia, anxiety, diarrhoea, eczema, headache, seasonal allergy, sinusitis, stomatitis and upper respiratory tract infection (each in 3 patients, 21.4%), abdominal pain upper, attention deficit hyperactivity disorder, constipation, cough, influenza, mouth ulceration, otitis media, pharyngitis streptococcal (each in 2 patients, 14.3%).

AEs suspected to be related to study drug were infrequent, each reported in only 1 (7.1%) patient, except stomatitis (reported in 3 patients, 21.4%).

One patient died during the study because of the AE of drowning; this death was considered as not related to everolimus.

Overall, SAEs were reported in 6 patients (42.9%) and all 6 patients had at least one grade 3 or 4 SAE.

None of the patients discontinued everolimus due to AEs. A total of 6 patients reported AEs that lead to dose adjustment of everolimus, out of which 3 patients had AEs that were ≥grade 3 in severity.

Of the AESIs included in the search strategy, only hemorrhage (3 patients, 21.4%) was reported in this study. None of the hemorrhage events were suspected to be treatment related. One patient had grade 3 hypofibrinogenaemia.

In summary, while the long-term safety data from study M2305 overall do not suggest a negative impact on growth and sexual development in paediatric patients previously treated with everolimus, no firm conclusions can be drawn due to the very limited number of patients included in the study. The safety profile was consistent with the known safety profile of everolimus in the TSC-SEGA patient population and no new safety signals were reported. Based on the results of the M2305 study, no changes to the SmPC were proposed nor considered necessary. However, it is recommended to monitor the effects on growth and sexual development in paediatric patients previously treated with everolimus and report it in the next PSURs (see also section 8).

7. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application. The (main) proposed RMP changes were the following:

The following significant changes have been made to the RMP version 16.0:

- Removal of safety concerns "Male infertility" (TSC setting only) and "Female infertility" (TSC setting only) as recommended by PRAC in the Final Assessment Report for Afinitor/Votubia RMP version 15.0.
- Completion of the additional PV activity, study CRAD001M2305, which was a category 3 study in the RMP.
- Removal of safety concerns "Postnatal developmental toxicity" (TSC setting only), "Long-term safety" (TSC setting only) and "Neurocognitive and sexual development in pediatric patients" (TSC setting only) as study CRAD001M2305 is now completed.
- The RMP is also aligned with new RMP template version 6.4 and updated with exposure data from latest PSURs for Afinitor and Votubia with DLP; 31-Mar-2024.

Therefore, there are no important identified risk, no important potential risks or missing information in the summary of safety concerns for Votubia remaining. Furthermore, there are no important identified/potential risks/missing information for Afinitor.

The proposed changes to the RMP are endorsed. Based on the completion of the additional PV activity, study CRAD001M2305, there are no further pharmacovigilance activities in place to further characterize the safety concerns "Postnatal developmental toxicity", "Long-term safety" and "Neurocognitive and sexual development in pediatric patients", respectively. Thus, the removal of these safety concerns from the RMP is acceptable in accordance with GVP module V - Risk management systems (Rev 2).
Referring to the final Assessment Report for Afinitor/Votubia RMP version 15.0 the removal of safety concerns "Male infertility" and "Female infertility" is supported, since no additional RMMs or pharmacovigilance activities are required for these risks. Furthermore, these risks are addressed in sections 4.6 and 5.3 of the EU-SmPC.
Finally, the update of the exposure data and the shift of study CRAD001M2305 from planned and ongoing studies to completed studies is endorsed.

The detailed changes to the RMP based on study CRAD001M2305 and removal of safety concerns is summarized in the table below.

Module/Annex	Summary of changes

Part II	
4.1 Module SIII Clinical trial exposure	- Updated of the clinical trial exposure
6.1 Module SV.1. Post-authorization exposure	- Updated of the post-marketing exposure
8.2 Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP	- Removal of the remaining safety concerns
8.3 Module SVII.3: Details of important identified risks, important potential risks, and missing information	- Removal of the details related to the safety concerns
8.3.1 Module SVII.3.1. Presentation of important identified risks and important potential risks	- Removal of the presentations since there are no safety concerns remaining
9 Module SVIII: Summary of the safety concerns	- Removal/Update of the list of safety concerns
PART III	
10.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection	- Removal of the specific adverse reaction follow-up checklists
10.2 Additional pharmacovigilance activities	- Removal of study CRAD001M2305 as this study is now completed.
10.3 Summary Table of ongoing and planned additional pharmacovigilance activities in the PhV Plan	- Removal of study CRAD001M2305 as this study is now completed.
Part V	
12.1 Description of routine risk minimization measures by safety concern	- Removal of risks as listed in Part II, update to reflect completion of study CRAD001M2305
12.3 Summary of pharmacovigilance activities and risk minimization activities by safety concerns	- Removal of risks as listed in Part II, update to reflect completion of study CRAD001M2305
Part VI	
13.2 II. Risks associated with the medicine and activities to minimize or further characterize the risks	- Removal of risks as listed in Part II
13.2 II.B: Summary of important risks	- Removal of risks and related descriptions as listed in Part II

13.2 II.C: Post-authorization development plan	- Removal of completed study CRAD001M2305
Part VII	
Annex 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study program	- Shift of study CRAD001M2305 from planned and ongoing studies to completed studies
Annex 3 Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan	- Removal of the protocol for completed study CRAD001M2305
Annex 4 Specific adverse drug reaction follow-up forms	- the specific adverse event follow-up checklists for Amenorrhea (Secondary amenorrhea) and Pregnancy were deleted
Annex 7 Other supporting data (including referenced material)	- References were updated
Annex 8 Summary of changes to the risk management plan over time	- Updated of the summary of changes with new version.

The MAH provided the final clinical overview on study CRAD001M2305. The RMP has been updated accordingly, taking into account that this study is now completed and is removed from ongoing PhV activities. The proposed changes to Parts II, III, V, VI and VII and Annexes of the RMP - based on completion of the study CRAD001M2305 - are considered acceptable. The removal of the safety concerns "Postnatal developmental toxicity", "Long-term safety" and "Neurocognitive and sexual development in pediatric patients" is endorsed, since no PhV studies are planned or ongoing to further characterize these risks. However, based on the low number of subjects included in study CRAD001M2305, these risks should be further monitored in future PSURs. In the currently ongoing PSUSA procedure for Votubia, the MAH is requested to monitor these safety concerns in future PSURs.

The removal of the specific adverse event follow-up checklists for Amenorrhea (Secondary amenorrhea) and Pregnancy from annex 4 of the RMP is endorsed as well.

Safety concerns

The following safety concerns have been removed from the summary of safety concerns since there are no further PhV activities in place after completion of study CRAD001M2305: "Postnatal developmental toxicity", "Long-term safety" and "Neurocognitive and sexual development in pediatric patients". The removal of these safety concerns is endorsed.

Pharmacovigilance plan

The proposed changes to Part III of the RMP (Pharmacovigilance plan) are listed in the table above. Study CRAD001M2305 was shifted from planned and ongoing studies to completed studies. A final clinical overview has been submitted for the study. This is endorsed.

Risk minimisation measures

No changes to the risk minimisation measures have been proposed based on the completion of the clinical study.

Annexes

The annexes have been updated appropriately.

7.1. Overall conclusion on the RMP

The changes to the RMP are acceptable.