23 July 2020
EMA/471889/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Votubia

International non-proprietary name: everolimus

Procedure No. EMEA/H/C/002311/II/0061

Note

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

Table of contents

1. Background information on the procedure 5
1.1. Type II variation 5
1.2. Steps taken for the assessment of the product 6

2. Scientific discussion 6
2.1. Introduction 6
2.1.1. Problem statement 6
2.1.2. About the product 8
2.1.3. The development programme/compliance with CHMP guidance/scientific advice 8
2.2. Non-clinical aspects 8
2.2.1. Ecotoxicity/environmental risk assessment 8
2.2.2. Discussion on non-clinical aspects 9
2.2.3. Conclusion on the non-clinical aspects 9
2.3. Clinical aspects 9
2.3.1. Introduction 9
2.3.2. Pharmacokinetics 10
2.3.3. Pharmacodynamics 10
2.3.4. PK/PD modelling 10
2.3.5. Discussion on clinical pharmacology 19
2.3.6. Conclusions on clinical pharmacology 19
2.4. Clinical efficacy 20
2.4.1. Discussion on clinical efficacy 22
2.4.2. Conclusions on the clinical efficacy 23
2.5. Clinical safety 23
2.5.1. Discussion on clinical safety 30
2.5.2. Conclusions on clinical safety 31
2.5.3. PSUR cycle 31
2.6. Update of the Product information 32

3. Benefit-Risk Balance 32
3.1. Therapeutic Context 32
3.1.1. Disease or condition 32
3.1.2. Available therapies and unmet medical need 32
3.1.3. Main clinical studies 33
3.2. Favourable effects 33
3.3. Uncertainties and limitations about favourable effects 33
3.4. Unfavourable effects 34
3.5. Uncertainties and limitations about unfavourable effects 34
3.6. Effects Table 34
3.7. Benefit-risk assessment and discussion 34
3.7.1. Importance of favourable and unfavourable effects 34
3.7.2. Balance of benefits and risks 35
3.7.3. Additional considerations on the benefit-risk balance 35
3.8. Conclusions 35

4. Recommendations..... 35

5. EPAR changes 36

List of abbreviations

AE	Adverse event
ACTH	Adrenocorticotrophic hormone
ADR	Adverse drug reaction
AML	(Renal) angiomyolipoma
BSA	Body surface area
Cmin	Trough concentration
Cmin_TN	Average concentration over a time interval in the last 12 weeks of the Core phase
CO	Clinical Overview
CS	Clinical Summary
CSR	Clinical Study Report
HT	High target
mTOR	Mammalian target of rapamycin
PBPK	Physiologically-based pharmacokinetic model
PD	Pharmacodynamics
PIP	Pediatric investigation plan
PK	Pharmacokinetics
PopPD	Population pharmacodynamics
PopPK	Population pharmacokinetics
POS	Partial onset seizures
PRR	Proportional reporting ratios
PT	Preferred term
PTY	Patient years
RR	Reporting ratios
RSF	Refractory seizure frequency
SEGA	Subependymal giant-cell astrocytoma
SF	Seizure frequency
SOC	System organ class
TSC	Tuberous sclerosis complex
VGB	Vigabatrin

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 27 August 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

To modify the approved therapeutic indication (adjunctive treatment of patients aged 2years and older whose refractory partial-onset seizures, with or without secondary generalisation, are associated with tuberous sclerosis complex, TSC) to include the new population of patients from 6 months to less than 2 years of age.

As a consequence, sections 4.1, 4.2, 5.1, 5.2 of the SmPC and sections 1 and 2 of the PL are updated accordingly.

Furthermore, the PI is brought in line with the latest QRD template version 10.1.

The variation requested amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

Information relating to orphan designation

Everolimus was granted an orphan designation by the EU (EU/3/10/764) on 04 August 2010 for the treatment of tuberous sclerosis. Everolimus has been authorised in the EU as Votubia since 2 September 2011.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0316/2017 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0316/2017 was completed. The PDCO issued an opinion on compliance for the PIP P/0316/2017.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	27 August 2019
Start of procedure:	14 September 2019
CHMP Rapporteur Assessment Report	8 November 2019
CHMP members comments	02 December 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	6 December 2019
Request for supplementary information (RSI)	12 December 2019
CHMP Rapporteur Assessment Report	8 April 2020
CHMP members comments	20 April 2020
Updated CHMP Rapporteur Assessment Report	24 April 2020
Request for supplementary information (RSI)	30 April 2020
CHMP Rapporteur Assessment Report	29 June 2020
CHMP members comments	13 July 2020
Updated CHMP Rapporteur Assessment Report	16 July 2020
Opinion	23 July 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The current variation seeks to extend the indication of TSC-associated refractory partial onset seizures (POS) which is approved for patients ≥ 2 years to patients as young as 6 months of age. This application

is based on extrapolated results for efficacy from available patient data in TSC studies already submitted during earlier procedures, and safety data from internal and external databases. No new clinical studies have been conducted for this application.

Biologic features

TSC is a rare and debilitating disease with a prevalence of approximately 1 in 6000 live births (Krueger and Franz, 2008). It is an autosomal dominant genetic condition involving the tuberous sclerosis 1 gene (TSC1) and/or the tuberous sclerosis 2 gene (TSC2). Deficiency of either gene leads to upregulation of mTORC1 resulting in abnormal cellular growth, proliferation, and protein synthesis, which can cause a variety of benign tumours, or hamartomas, in multiple organ systems including lesions in the kidney, brain, skin, lung and heart.

Neuropathologic lesions of TSC include subependymal nodules, subependymal giant-cell astrocytoma (SEGA), cortical hamartomas, areas of focal cortical hypoplasia and heterotopic gray matter (Takanashi et al 1995, Weiner et al 1998). The predominant neurological manifestations of TSC are mental retardation, epileptic seizures and behavioural abnormalities (Gomez 1999, Curatolo 2003, Chu-Shore et al 2010).

Clinical presentation, diagnosis and stage/prognosis

Epileptogenesis in TSC can start far before birth. Mutation of TSC1/2 genes leads to overactivity of the mTOR (mammalian target of rapamycin) pathway, which can predispose to epilepsy. These changes can appear during fetal life (Overwater et al 2015, Moavero and Curatolo, 2018).

Epilepsy is a common manifestation of TSC, affecting up to 85% of patients. The majority (63%) of TSC patients experience seizure onset within the first year of life. In early onset, epilepsy may manifest as infantile spasms or focal (partial) seizures, which can coexist (Chu-Shore et al 2010). Early management of seizures is important in preventing subsequent epileptic encephalopathy and in reducing the cognitive and neuropsychiatric consequences (Davis et al 2017, Moavero and Curatolo, 2018, Wang and Fallah, 2014).

Refractory seizures (resistant to first-line pharmacological interventions like vigabatrin, adreno-corticotrophic hormone, and other anti-epileptic drugs acting on the GABA pathway) occur in up to 67% patients. There are only a few studies with sufficiently large sample size focused on infants with TSC and epilepsy. In a study to assess the response to anti-epileptic drugs (19 in total) in 71 children with TSC, only 30% patients achieved remission beyond 24 months. In another study with 122 children, where the youngest child was 2 months of age, significant seizure-free remission was achieved in not more than 14% children (Sparagana et al 2003, Moavero and Curatolo 2018, Overwater et al 2015).

Management

Seizures associated with TSC are treated with antiepileptic drugs (AEDs) or methods such as epilepsy surgery, vagal nerve stimulator or ketogenic diet. Other than for infantile spasms in TSC for which vigabatrin is usually recommended as first line treatment, there is little evidence to guide effective anticonvulsant treatment. The published literature suggests that TSC-associated partial onset seizures (POS) may respond to one or several AEDs approved for the treatment of POS, e.g. topiramate, lamotrigine, levetiracetam, oxcarbazepine, and clobazam. The prevalence of medically refractory epilepsy in TSC even with adequate trials of currently available anticonvulsant medications has been reported as high at approximately 60% (Jobst 2009; Wong 2010).

2.1.2. About the product

Votubia contains the active substance everolimus, an antineoplastic and immunomodulating agent with currently two ATC codes (L01XE10 and L04AA18 respectively), which acts as selective inhibitor of the mammalian target of rapamycin (mTOR), a serine-threonine kinase within the mTOR-raptor signal transduction complex 1 (mTORC1) which is involved in the regulation of protein synthesis, cell growth, proliferation and survival. Due to its immunosuppressing activity, everolimus was initially developed to prevent allograft rejection following solid organ transplantation. In the EU, everolimus is approved under the tradename Afinitor for the treatment of patients with advanced renal cell cancer, advanced neuroendocrine tumours, and hormone receptor-positive advanced breast cancer.

Votubia has been authorised in the EU/EEA through the centralised procedure by Commission Decision in September 2011 for treatment of (renal angiomyolipoma [subject to a later variation] and) subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC). It is available as tablets (2.5, 5 and 10 mg) and dispersible tablets (1, 2, 3 and 5 mg). Everolimus dispersible tablets under the trade name Votubia received approval from the European Commission in January 2017 for a third TSC manifestation, i.e. adjunctive treatment of patients aged 2 years and older whose refractory partial onset seizures (POS), with or without secondary generalization, are associated with TSC. This approval was based on the results of Study CRAD001M2304 (also referred as M2304, or EXIST-3), a Phase 3 study including 294 paediatric patients aged 2-18 years with TSC-associated refractory POS.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

On 23-Jan-2013, the European Medicines Agency agreed on a PIP for 'refractory epilepsy associated with TSC' and granted a deferral to everolimus (P/0012/2013). In 2017, the PIP was modified (EMEA-C-000019-PIP08-12-M03). A study in patients less than 2 years of age with infantile spasm was removed, and a modelling and simulation study, which extrapolates data from existing studies to the target population, was added in order to complete the paediatric development of everolimus in patients below the age of 2 with refractory POS associated with TSC. The proposed models incorporated a physiologically-based pharmacokinetic model (PBPK) to predict everolimus PK parameters in patients 6 months to 1 year of age, a population pharmacokinetic (popPK) and population PD (popPD) model to predict short-term efficacy, and an exposure-efficacy linear mixed model to predict long-term efficacy. In effect, the proposed models would evaluate efficacy in patients between 6 months to 2 years of age.

In addition, a waiver was granted for patients from birth to <6 months of age on the grounds that everolimus does not represent a significant therapeutic benefit in the treatment of infantile spasms over existing treatments.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

According to EMEA-000019-PIP08-12-M02 and P/0316/2017, a non-clinical evaluation is not applicable.

2.2.1. Ecotoxicity/environmental risk assessment

The applicant submitted an environmental risk assessment on the active ingredient everolimus dated on August 2019 consisting of a justification for not providing an updated environmental risk assessment in the current Type II Variation.

2.2.2. Discussion on non-clinical aspects

A complete ERA for the active ingredient everolimus was provided within procedure EMEA/H/C/2311/II/41 in 2016. Everolimus was not considered to pose a risk to the environment. Since the PEC calculations in the above-mentioned ERA were based on a fraction of market penetration (Fpen) of 0.01, representing 1% of the population also the patient population aged 6 months to 2 years was included in these calculations.

Based on the provided data, everolimus is not considered to pose a risk to the environment including surface waters, sewage treatment plants, groundwater, terrestrial compartments and sediments.

2.2.3. Conclusion on the non-clinical aspects

This application does not lead to a significant increase in environmental exposure further to the use of everolimus.

2.3. Clinical aspects

2.3.1. Introduction

In the EU, Everolimus is currently approved in three TSC manifestations:

- SEGA (in adult and paediatric patients; however, the safety, efficacy and pharmacokinetic profile of Votubia in children below the age of 1 year with TSC who have SEGA have not been established),

- renal angiomyolipoma (in adult patients only), and

- adjunctive treatment of refractory partial-onset seizures (POS) in (adult and paediatric) patients aged 2 years and older.

The applicant is now seeking extension of the indication of TSC-associated refractory POS from adults and children aged 2 years and older to children as old as 6 months of age.

The clinical studies in TSC patients supporting this application have been submitted previously. No new studies have been performed for this submission. The efficacy and safety data relevant to patients between 6 months and 2 years of age are obtained from modelling and simulation exercises and safety databases. The clinical trials summarized in the following table served as the source for these exercises; they are not used directly to impute the conclusions of the MAH.

Table 1: Overview of TSC studies used for modelling and simulation

Study No.	Details	Number of patients	Number of patients below 18 years of age
[Study M2304]	A three-arm, randomized, double-blind, placebo-controlled study of the efficacy and safety of two trough-ranges of everolimus as adjunctive therapy in patients who have refractory TSC-POS.	366	147
[Study M2301]	A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of patients with SEGA associated with TSC. A study with a Core phase with two arms everolimus vs. placebo and a long term evaluation phase with everolimus only.	111	59
[Study M2302]	A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of renal angiomyolipoma in patients with either TSC or sporadic LAM. A study with a Core phase with two arms everolimus vs. placebo and a long term evaluation phase with everolimus only.	118	0

GCP

The clinical studies in subjects with TSC supporting this application have been submitted previously. No new studies have been performed for this submission. The Clinical trials were performed in accordance with GCP as claimed by the MAH.

2.3.2. Pharmacokinetics

Since the development of the PBPK model is linked to the subsequent exposure-response models, model development and evaluation of all developed models can be found under 2.3.4. PK/PD modelling.

2.3.3. Pharmacodynamics

n/a

2.3.4. PK/PD modelling

Objectives
The proposed modelling and simulation study is aimed at completing the paediatric development by predicting exposure in patients 6 months old to 1 year of age (target population for PK) and everolimus efficacy in patients from 6 months to less than 2 years of age (target population for efficacy). The predicted exposure and efficacy, is used to justify the safe and efficient use of everolimus in patients between 6 months and 2 years.

M&S approach
The modelling and simulation framework consists of 3 different models that were used in conjunction to enable the prediction of precise and reliable pharmacokinetic and pharmacodynamic markers in children between 6 months and less than 2 years of age. The first model, a physiology-based pharmacokinetic (PBPK) model was built and qualified using currently available PK data in children (≥1 year of age) and adults using the Simcyp® simulation software. The PBPK model was used to predict Cmin exposure in paediatric patients. This Cmin exposure was then be used as regressor to predict the response

(percentage reduction from baseline in seizure frequency). The response was predicted using two exposure-response models, a population pharmacodynamic model and a linear mixed effect model. These models were built upon the PD data from study M2304, because this is the only study with POS. These models were used to predict the short-term and long-term efficacy in patients under 2 years.

These three models were developed based on data from three clinical trials which enrolled patients in the TSC setting. These data were used to validate the models before performing the predictions:

- Study CRAD001M2301 with patients 1 year of age and older with SEGA associated with TSC, to provide pharmacokinetic data. Youngest patient's age: 1.1 year, n=10 patients between the age of 1-2 years.
- Study CRAD001M2302, performed in the adult population with renal AML associated with TSC, to provide pharmacokinetic data.
- Study CRAD001M2304 (core phase analysis) with patients 2 years and older with refractory POS associated with TSC, to provide pharmacokinetic and short-term pharmacodynamics data. Study CRAD001M2304 (Extension analysis) with patients 2 years and older with refractory POS associated with TSC, to provide pharmacokinetic and long-term pharmacodynamic data.

Table 3-1 Study number, design, population and corresponding data and reports to be used in the bridging measure

Study	Study design	Source population (sample size, age)	Used for following analyses in the bridging measure
[CRAD001M2301 core and final clinical study reports]	Double-blind, randomized, parallel-group, placebo-controlled, multicenter trial efficacy/safety in patients with TSC who have SEGA (with 2:1 randomization for everolimus: placebo)	**Core Phase**: N=117 patients: 78 treated with everolimus, 39 Placebo. **Core and Extension** N=111 patients treated with everolimus. **Ages**: < 3 (18), ≥3-<10 (41), ≥10-<18 (34), ≥18 (18). The youngest patient was 1.1 year (no age restriction in the protocol). The study enrolled 10 patients between the age of 1 and 2.	Pharmacokinetics Safety
[CRAD001M2301 PK expert report – PK sub-study results]	Post-authorization measure – Pharmacokinetics in children CRAD001M2301 PK sub-study results	PK profiles of 33 patients. 11 patients from 3 to 10 years, 13 from 3 to 18 years, 9 patients 18 yrs or older.	Pharmacokinetics
CRAD001C2485 data	Non-randomized, single-arm, open-label trial Efficacy/safety in patients with TSC who have SEGA	N=28 patients treated with everolimus. **Ages**: 3 to <12 (16), > 12 to < 18 (6), ≥ 18 (6). Youngest patient 3 yrs. (protocol inclusion criteria specified a minimum age of 3)	Pharmacokinetics Safety
CRAD001M2302 data	Double-blind, randomized, parallel-group, placebo-controlled, multi-center trial Efficacy/safety in adult patients with TSC or sporadic LAM who have angiomyolipoma (with 2:1 randomization for everolimus: placebo)	N=118 patients: 79 treated with everolimus, 39 Placebo. **Ages**: Adult patients	Pharmacokinetics Safety
[CRAD001M2304 CSR Core Analysis] [CRAD001M2304 CSR Extension Analysis]	A three-arm, randomized, double-blind, placebo-controlled study of the efficacy and safety of two trough-ranges of everolimus as adjunctive therapy in patients with tuberous sclerosis complex who have refractory partial-onset seizures	**Core Phase**: N=366 patients: 247 treated with everolimus, 119 Placebo. **Ages**: <6 (104), =>6-<12 (113), =>12-<18 (82), =>18-<65 (67). The youngest patient was 2 years. **Core and Extension** N=361 patients treated with everolimus. <6 (101), =>6-<12 (109), =>12-<18 (84), =>18-<65 (67). 22 patients with ages between 2 and 3. The youngest patient was 2 years (initial protocol specified the age range 2-65 years, but was amended to include patients from 1 year of age in Europe)	Pharmacokinetics Safety Efficacy Exposure-efficacy Exposure-safety

Background

Everolimus is primarily eliminated by metabolism via CYP3A4 and is a substrate for PgP. Data in patients with TSC suggested that everolimus clearance was lower in younger patients, while BSA-normalized everolimus clearance was higher in younger patients as indicated by dose-normalized Cmin.

The approved dosing method consists of starting doses and the pre-dose everolimus concentration range for therapeutic drug monitoring for patients with TSC-SEGA and TSC-seizures.

PBPK model

Model building

The software Simcyp was used for model building and simulations. An adult PBPK model was built to predict everolimus PK after single and multiple doses and to ensure proper definition of its clearance pathways using the available clinical mass-balance and *in vitro* phenotyping and clinical DDI data with CYP3A4 perpetrators. The developed PBPK model was then qualified to predict the adult TSC patient PK data from trials CRAD001M2301, CRAD001M2302, and CRAD001M2304, including PK parameters measured in the sub-study of CRAD001M2301.

These adult PBPK model RAD001 (everolimus) compound file input parameters were first used in the paediatric Simcyp model (where demographics, physiology, and ontogeny of clearance pathways vary with age). However, there was a consistent under-prediction of Cmin and over-prediction of the apparent Cmax across the ages and dose groups when the Simcyp paediatric model was used. An improvement was made using a more recently published ontogeny for CYP3A4 (Upreti and Wahlstrom 2016) rather than the current ontogeny in the Simcyp paediatric model. The apparent Cmin values were improved; however, the Cmax values were still over-predicted, particularly for subjects <12 years of age. For subjects < 12 years of age, the absorption parameter, fa, was reduced to 0.5 (from fa=1 in adults) and distribution parameters were also adjusted. For subjects < 12 years of age, distribution parameters were based upon simultaneous parameter estimation simulations in Simcyp. The applicant stated that although the reason for the modification of absorption and distribution parameters of RAD001 for the younger paediatric population is unclear, it may be a combination of RAD001 distribution into higher fat content in children compared to healthy adults and the potential greater impact of food intake on the absorption of RAD001 in children. The model was built originally for healthy adult volunteers in a fasted condition. There is a negative food effect with low fat food reducing the AUC by 30-32% and Cmax by 42-50% (regular or dispersible tablets) and, for the trials used in the qualification, RAD001 could be taken just after a low fat meal (M2301, M2303, M2304). The modifications of the absorption and distribution parameters were deemed appropriate by the applicant to simulate the apparent Cmax and Cmin concentration values across the pediatric age range of 1 to <12 years of age and across the examined dose ranges.

Model evaluation

The PBPK model for RAD001 was developed first to simulate the single and multiple dose PK of RAD001 in adults. The observed and simulated PK parameters for RAD001 after single oral doses (2 and 4 mg) in healthy volunteers were compared. All the PK parameters were predicted within 2-fold of the actual value (prediction errors < -50% and > +100%).

The PBPK model was also built to predict the magnitude of the interaction of RAD001 with CYP3A4 perpetrators ketoconazole, erythromycin, and rifampin. All PK parameters were predicted within 2-fold of the actual values and the DDI (AUC and Cmax ratios) were predicted within 40% of the actual values and within the criteria outlined in Guest et al 2011. Therefore, the contribution of CYP3A4 to the clearance of RAD001 in adults was deemed to be well defined.

The PBPK model was then qualified to predict the PK of RAD001 in adult TSC patients. All simulated parameters were predicted within a prediction error <40%.

After refinement of the model for paediatric use, the observed individual patient data from Study CRAD001M2301 and from Study CRAD001M2304 were compared to the predicted concentrations.

The ages were grouped: 1-3 years, 3-6 years, 6-12 years, and 12-18 years.

In table 6-5 (for the ages from 1 to >18 years) and table 6-7 (for ages 3 to <10 years) PBPK-simulated PK parameters are compared with the population PK results (RAD001 PopPK Report 2017). Particularly for the young ages (ages 1-12 years), the PBPK model simulated the mean BSA corrected blood CLpo and ratio of the clearances in children versus adults with a prediction error within ~ ±10%. For older children (age 12-18) the simulations had a prediction error of ~ -30%.

Table 6-5 Summary statistics of BSA-corrected CL_{po} (or CL/F) by age group

Age group	Model	Mean blood CL_{po} (L/h) (PE%)	Mean BSA corrected blood CL_{po} (L/h/m^2) (PE%)	Mean BSA corrected blood $CL_{po_{child}}/CL_{po_{adult}}$ (PE%)
<3 (i.e. 1-3)	PopPK[a]	12.3 ± 5.2	20.7 ± 7.8	1.52
	PBPK[b]	12.2 ± 8.0 (-1%)	21.3 ± 13.1 (+3%)	1.65 (+8.6%)
3-6	PopPK	18.01 ± 6.27	24.28 ± 8.68	1.78
	PBPK	16.2 ± 10.4 (-10%)	22.5 ± 13.8 (-7.3%)	1.74 (-2.2%)
6-12	PopPK	21.3 ± 8.04	20.6 ± 7.50	1.51
	PBPK	23.0 ± 14.7 (+8%)	22.1 ± 13.5 (+7.2%)	1.71 (+13%)
12-18[c]	PopPK	27.9 ± 10.8	18.9 ± 8.1	1.38
	PBPK	19.8 ± 12.9 (-29%)	12.4 ± 7.31 (-34%)	0.96 (-30%)
≥18	PopPK	24.9 ± 9.54	13.7 ± 5.25	
	PBPK	24.0 ± 15.7 (-3.6%)	12.9 ± 8.03 (-5.8)	

PE%, prediction error % = [(predicted value – observed value)/observed value]*100

[a]Source data: (RAD001 PopPK Report 2017)

[b]PBPK model: 2 mg dose to steady-state, 50 trials of 20 subjects (n=1000)

[c]The compound file used for this age group did not have modified absorption or distribution parameters as those <12 years of age. The compound file used for this age group was the same as that used in the adult PBPK model. Using the model with adjusted absorption and distribution parameters for this age group resulted in similar PE% values for the ratio of BSA corrected (+29% error), *data not shown*.

Table 6-7 Observed versus simulated RAD001 multiple dose PK parameters in pediatric TSC patients (3 to <10 years of age) in the absence of CYP3A4/P-gp perpetrators

PK parameter		Value (PE%)
C_{min}/Dose	Observed (n=5)[a]	1.51 ± 1.4
	Simulated (n=1000)[b]	*1.56 ± 1.2 (+3.3%)*
AUC_{0-24}/Dose	Observed (n=5)	73.7 ± 43
	Simulated (n=1000)[b]	*65.4 ± 40 (-11%)*
C_{max}/Dose	Observed (n=5)	8.65 ± 4.5
	Simulated (n=1000)[b]	*7.51 ± 7.1 (-13%)*

Units are: AUC, ng/mL*h/mg; C_{max} and C_{min}, ng/mL/mg

PE%, prediction error % = [(predicted value – observed value)/observed value]*100

[a]Source data for clinical PK parameter results: CRAD001M2301 PK sub-study results Appendix 1 Tables, Figures and Listings (2013), Table 14.5-8.4. PK values in the presence of no CYP3A4/P-gp inhibitors or inducers. Values are the dose normalized arithmetic mean ± standard deviation (SD).

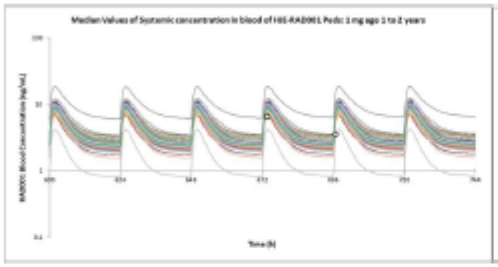
[b]Simcyp simulated results of age group 3-10 years, 10 mg RAD001 dose arbitrarily selected (PK parameters are dosed normalized), 50 trials of 20 subjects (n=1000). Values are the dose normalized arithmetic mean ± SD.

For the youngest investigated patients (1-2 years) PBPK-simulated and observed concentrations are depicted in figure 8-5.

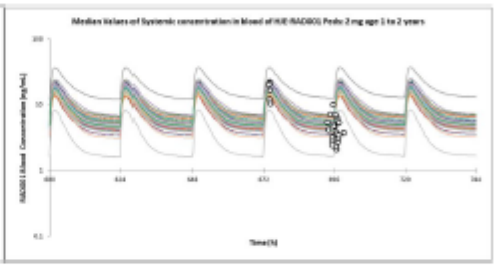
Figure 8-5 Simulated concentration-time profiles of RAD001 in pediatric TSC patients age 1-2 years with various RAD001 doses

The colored lines are the PBPK predicted RAD001 concentrations of the trial medians (50 trials of 20 subjects) and upper and lower 95th/5th percentiles (upper and lower grey lines, respectively). The observed individual patient data (open circles, from Study RAD001M2301) is plotted as time after dose during steady-state.

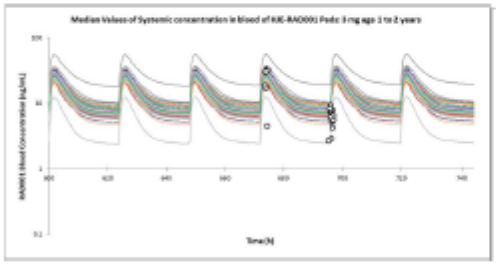
1 mg



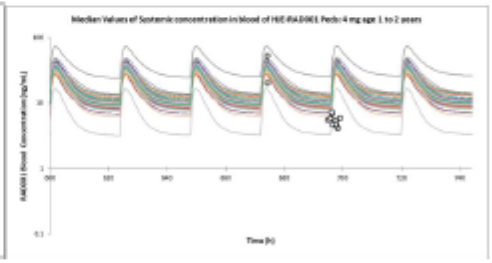
2 mg



3 mg



4 mg



5 mg

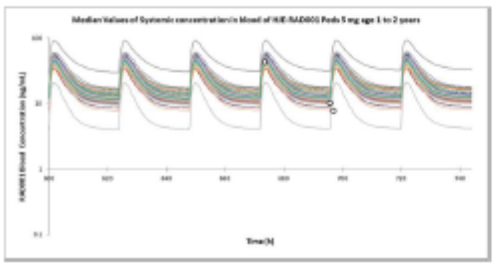
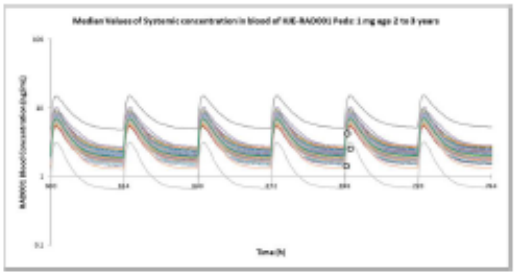


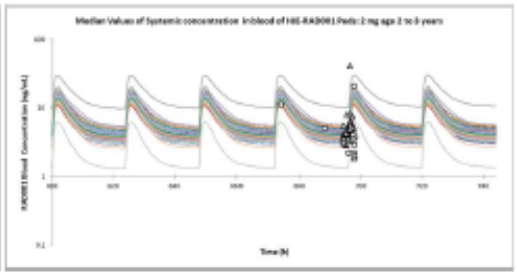
Figure 8-6 Simulated concentration-time profiles of RAD001 in pediatric TSC patients age 2-3 years with various RAD001 doses

The colored lines are the PBPK predicted RAD001 concentrations of the trial medians (50 trials of 20 subjects) and upper and lower 95th/5th percentiles (upper and lower grey lines, respectively). The observed individual patient data (open circles from Study RAD001M2301; open triangles from Study RAD001M2304) is plotted as time after dose during steady-state.

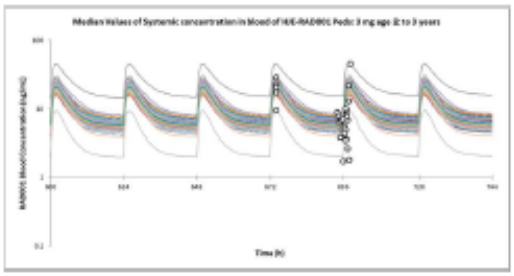
1 mg



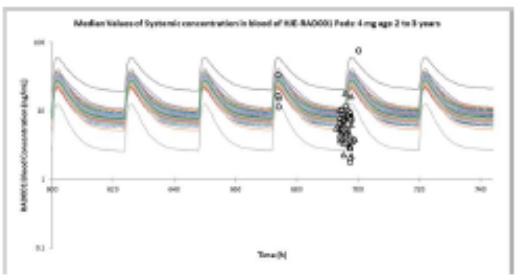
2 mg



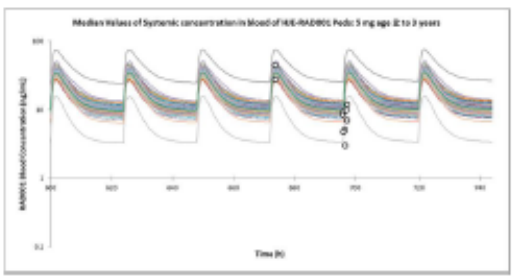
3 mg



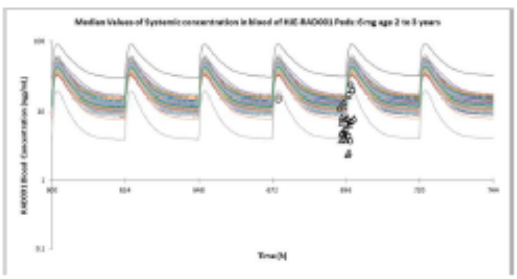
4 mg



5 mg



6 mg



PopPK model

The PopPK model was developed from a previous model with a two-compartment structure with first-order absorption (ka) and elimination (Cl), developed based on data from the extension of study [CRAD001M2301 population PK - 5 years update]. This model was evaluated using pooled data from Studies M2301, M2302, and M2304 (core and extension phase) that included 7,262 observations from 539 patients, the youngest age being 1 year old. The population PK model adequately described the data from studies M2301, M2302, and M2304. Time-varying CYP3A4 inducer status was retained as covariate on central clearance (Cl), and time-varying BSA was on all parameters related to volume and clearance. Mean clearance, either associated or not with the use of a CYP3A4 inducer, was positively related to age. When corrected by body surface area (L/h/m2), the mean clearances were near 20 L/h/m2 with a slight decrease with increasing age. Adults without inducers had a lower mean BSA-corrected clearance of 13.66 L/h/m2. Body surface area corrected CL demonstrated consistent variability over the age range, with and without inducer, with a coefficient of variation of 30- 40%. This model, was used for Cmin prediction in the pharmacokinetic/pharmacodynamic analysis.

Exposure-response

Pharmacodynamic modelling of everolimus effect on refractory partial-onset seizures associated with tuberous sclerosis complex aimed at assessing the efficacy of everolimus when Cmin is included within 5 to 15 ng/mL. Three different models were developed to evaluate this relation.

Prediction of short-term efficacy

The PKPD model consisted of three submodels: the baseline model, the placebo model and the everolimus model.

The baseline disease was developed using the screening phase data, before administration of the first dose (either placebo or everolimus) for all patients. Demographic covariate (age, body surface area, Race, Gender and comedications) effects on mean number of seizures were assessed. The placebo effect was added in addition to the baseline model and demographic/comedications effects. The everolimus effect was added by analyzing the entire dataset, with patients in the everolimus arm and patients in the placebo arm after they switched to everolimus. Demographic covariate (age, body surface area, Race, Gender) effects on everolimus effect parameters were assessed. Finally, daily Cmin concentration at the time of seizure recording was predicted for all patients after first everolimus administration based on the population PK model described previously and the dose and time of dose as reported during the study. Model simulation and fitting were performed in Monolix Suite 2016R1 on the Novartis MODESIM high performance computing environment accessing data from the GPSII system. Model fitting was conducted using the SAEM algorithm of Monolix. Matlab 2012a was used for simulations.

The final selected model was an Emax effect model where the maximal value of the effect increased to a maximal value of 1 following an exponential equation. This asymptotic exponential equation was driven by the time since the first everolimus administration and an estimated parameter describing the log-slope of Emax increase.

Covariate model

Sex, age, BSA and race effects were tested in a forward-selection process. The only factor deemed to influence significantly the baseline was the age at start of screening, where children tended to experience more seizures than adults. The model also identified an effect of age on the everolimus effect. Time to reach everolimus maximal effect was predicted to increase with increasing age; everolimus, therefore, should attain its maximal effect faster in children than in adults.

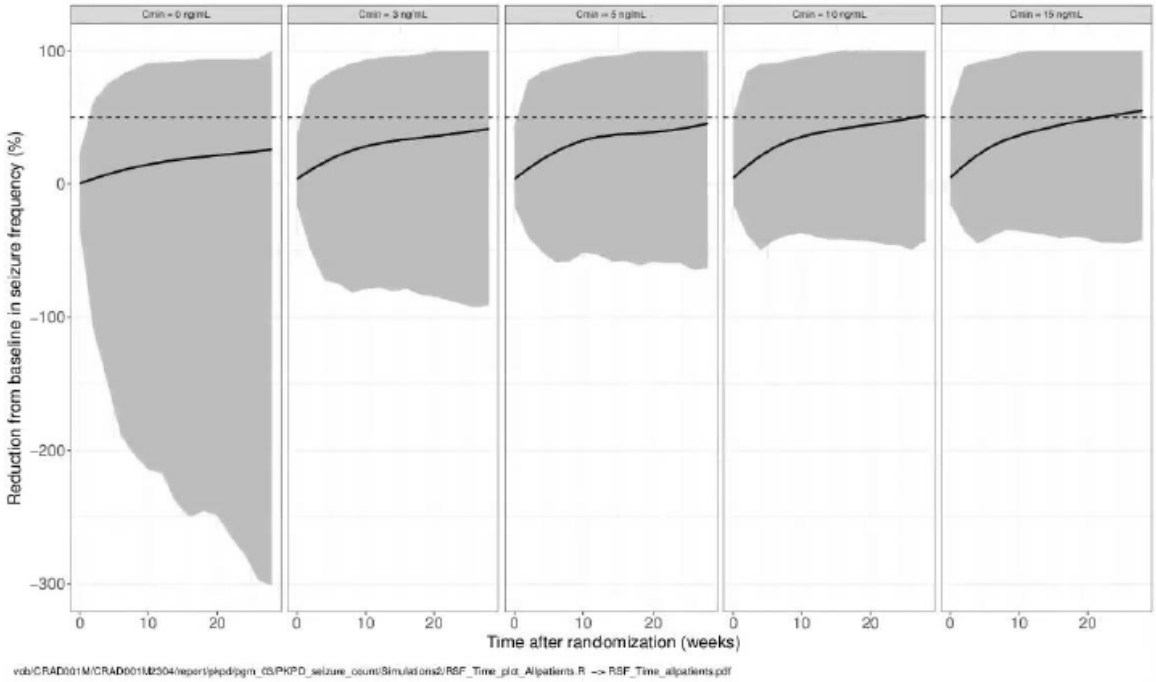
A change in age from the median value of 10.1 years to 6 or 18 years would modify the half-life of EmaxEVE,i,d from 122.1 weeks to respectively 70.7 and 224 weeks. Inclusion of a second covariate did not improve the model fit.

The final model was used to explore the relation between the exposure (Cmin) and the predicted percentage reduction from baseline in seizure frequency. Percentage change from baseline for each patient in study M2304 was predicted using the individual estimates from the final model. Also, the predicted proportion of responders for each scenario were computed (>50% reduction from baseline in seizure frequency).

The response rate for patients under placebo is about 30% and increased with the everolimus Cmin concentration. With Cmin concentrations above 5 ng/mL, the median expected response rate range from 30% to 50%: The median proportion of responders is positively correlated with Cmin. The curve depicting the median proportion of responders appears approximately piecewise linear, with a steeper slope before 5 ng/mL, suggesting an advantage to targeting Cmin values of 5 ng/mL or greater. There are responders

patients at low everolimus exposure (Cmin as low as 0.5 ng/mL), while other patients would require higher everolimus concentrations or a longer treatment. There were also responders among the patients treated with placebo only. A concentration of 3 ng/mL was associated with a slightly lower median proportion of responders than 5 ng/mL, but the uncertainty was large.

Figure 5-10 **Predicted percentage reduction from baseline in seizure frequency of responders versus time for selected Cmin values.**



Grey area represents the 5-95% Prediction Interval around the 50th percentile of the predictions (black line). Dashed line represents the 50% reduction from baseline threshold for responders.

Predicted Cmin associated with a 50% reduction from baseline in seizure frequency at 6 months justified the target range of 5 to 15 ng/mL in this indication. The results support the use of the everolimus target range of 5 – 15 ng/mL given the inter-subject variability observed in the exposure-response relationship and the absence of enough safety data for Cmin values above 15 ng/mL.

Prediction of long-term efficacy

For prediction of long-term efficacy, two different models (Model A and B) were developed.

Model A: A multiplicative linear regression model for post-baseline SF was used. In this model, the post-baseline SF after a fixed time interval (12 weeks) was linked to the time-normalized Cmin over the 12 weeks intervals, accounting for the longitudinal nature of the data.

The parameter estimates from this model fitted on the M2304 data first were used to predict post-baseline TSC-associated refractory seizure frequency in the simulated patient population for ten scenarios where the subjects started treatment at 6 months old up to 2 years old and were treated for a period of 2 years (96 weeks). The model considered log-transformed SF at baseline, the number of days the patient was on everolimus treatment and log-transformed time-normalized Cmin as covariates and patient as random effect. A random subject effect on the slope of days on everolimus treatment is also included. An unstructured covariance structure is assumed for the random effects.

Model B: The exposure-efficacy relationship was explored by a multiplicative linear regression model for the ratio of post-baseline and baseline SF (SF/SFB) considering time-normalized Cmin over 12 week intervals. The factor "time", i.e. the number of days the patient was on everolimus treatment and the log-transformed time-normalized Cmin as covariates and patient as random effect were included in the model. An additional random subject effect on the slope of days on everolimus treatment is also included. An unstructured covariance structure is assumed for the random effects.

Both linear mixed models (Model A and Model B) allowed the prediction of postbaseline seizure frequency. The Model B results were consistent with the Model A results. Time-normalized Cmin and the time of exposure to everolimus were found to influence the long-term efficacy of everolimus in reducing the post-baseline SF to baseline SF ratio (SF/SFB). The reduction effect on the post-baseline SF to baseline SF ratio (SF/SFB) was estimated to be 21.44% (95% CI from 13.36 to 28.77) for every 2-fold increase in Cmin and 5.64% (95% CI from 3.54 to 7.70) for every additional 12 weeks on everolimus treatment.

Exposure-efficacy analyses predicted that TSC patients between 6 months and 2 years old would experience a reduction in TSC-associated refractory seizure frequency at both short-term and long-term exposures. In fact, this effect could be seen as early as 12 weeks into therapy when patients have reached steady state. The predicted median reductions in seizure frequency were in the range of 40% to 70%, more noticeable among younger patients. These results are higher than the reduction in baseline seizure frequency actually observed in study M2304 in adult patients (30% to 40%), which can be expected given the higher steady state Cmin observed in patients of 6 months to 2 years of age. Additionally, PopPD models included an age effect, leading to a quicker response in children. From the long-term efficacy analysis based on the M2304 data, seizure control was assumed to improve with continued therapy with everolimus, and thus increased reductions in seizure frequency were predicted with continued exposure for up to 2 years (96 weeks).

2.3.5. Discussion on clinical pharmacology

A PBPK model has been developed with the available adult data and has been refined for paediatric patients. This model is intended to be used to predict PK parameters in children aged 6 months to 1 year. PBPK modelling incorporates age-related differences in demographics, physiology, and ontogeny of clearance pathways. Since everolimus is mainly metabolized by CYP3A4, CYP3A ontogeny was implemented in the model according to a recent publication (Upreti and Wahlstrom, 2016). Nevertheless, CYP3A ontogeny during the time between 6 months and 1 year is very steep, thus bearing high uncertainty when predicting Cmin concentrations. Due to the high uncertainty it is not considered possible to reliably reach the necessary specific target range of Cmin concentrations with this model.

In addition, the PBPK model was used to generate Cmin concentrations for children aged 1-2 years to be used as input for exposure-response modelling. With the currently developed model it remains unclear whether the Cmin concentrations are adequately predicted.

It was agreed that section 5.2 of the SmPC should reflect that in patients with TSC and refractory seizures, Votubia concentrations were investigated in n=9 patients in the age between 1 and<2 years. Doses of 6 mg/m2 (absolute doses range 1-5 mg) were administered and resulted in minimal concentrations between 2 and 10 ng/ml (median of 5 ng/mL; total of >50 measurements). No data are available in patients with TSC-seizures below the age of 1 year.

2.3.6. Conclusions on clinical pharmacology

The currently presented PBPK model is not considered adequate to generate valid PK parameters in patients aged 6 months to 1 year and Cmin concentrations in patients aged 1 to 2 years in order to be

used as input to subsequent exposure-response models. Nevertheless, addition of relevant information on concentration data generated in children aged 1-2 years to section 5.2 of the SmPC was agreed.

2.4. Clinical efficacy

No clinical studies evaluating efficacy of everolimus for treatment of POS in TSC patients aged 6 month to 2 years are available. Efficacy in this indication is intended to be extrapolated from children above 2 years of age and adults (source population) to patients aged 6 months to 2 years (target population) via modelling and simulation exercises based on previously submitted TSC studies. As shown in Table 1, above, study M2304 results were modelled to predict efficacy of everolimus in patients aged 6 month to below 2 years with TSC associated POS. In addition to study M2304, studies M2301 (the pivotal study in TSC patients with SEGA, which included paediatric and adult patients, including overall 10 patients between the age of 1 and 2 years) and M2302 (the pivotal study in adult patients with renal angiomyolipoma) were used to develop the PBPK model.

For further assessment of the PBPK modelling, population PD modelling as well as the linear mixed effect modelling, please refer to Pharmacokinetics and Pharmacodynamics sections of this report (sections 2.3.2 and 2.3.3., above).

Justification for extrapolation of efficacy

The following information regarding TSC associated refractory partial onset seizures (POS) in the target population was presented in the submitted Clinical overview. The main argument presented by the applicant in the Clinical overview in support of extrapolation of efficacy is that due to the common aetiology of TSC-refractory POS and presence of the same targets in patients between 6 months and 2 years of age, everolimus is expected to be effective and safe in this target population as it has been demonstrated in patients older than 2 years of age.

In addition, further information is given in the Bridging Concept:

In a Massachusetts General Hospital retrospective study that included all children and adults with TSC seen between Jan-2002 and Oct-2008 (291 patients), the most common seizures observed were complex partial seizures (86.9%, including those with secondary generalization) and infantile spasms (46.4%). The onset of seizures typically occurs in the first year of life (with 63% within 1 year of age and 82% before 3 years of age); however, adults remain at risk and up to 12% of adult patients with TSC develop epilepsy as adults, indicating that TSC patients are at an increased risk of epilepsy throughout their lifetime (Chu-Shore et al., 2010). No report on noteworthy differences in POS types between age groups has been found.

According to the Bridging Concept, treatment of POS in TSC is similar to POS resulting from other causes and TSC-seizures might respond to AEDs indicated for POS (such as topiramate, lamotrigine, levetiracetam, oxcarbazepine, and vigabatrin). The guidelines for AED treatment are generally the same for children and adults, i.e., the AED strategy should be individualized according to seizure type, epilepsy syndrome, co-medication and co-morbidity (Krueger and Northrup 2013).

Efficacy in source population:

Everolimus has been approved for treatment of TSC associated POS in patients aged ≥ 2 years based on one pivotal study (M2304). Study M2304 was a double-blind, randomized, multi-centre, Phase III trial evaluating the efficacy and safety of two different target trough ranges of everolimus in patients (aged 1 to 65 years in Europe, and 2 to 65 years for the rest of the world) who have refractory TSC-associated POS while being on a stable regimen of 1 to 3 AEDs.

The design, including the choice endpoints, was generally in line with the recommendations of the CHMP guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (CHMP/EWP/566/98Rev.2/Corr) on confirmatory studies in adjunctive treatment of refractory seizures.

Short-term efficacy:

During the 12 week maintenance period of the core phase, Study M2304 demonstrated superiority of everolimus at two target through ranges (LT: 3 to 7 ng/mL and HT: 9 to 15 ng/mL) over placebo in reducing the frequency of TSC seizures in both paediatric and adult patients with refractory epilepsy. Statistically significantly higher 50% responder rates (difference to placebo: 13.1% and 24.9% for LT and HT, respectively) as well as percent reduction in weekly TSC seizure frequency from baseline (difference to placebo: 16% and 27.5% for LT and HT, respectively) were found for both tested everolimus groups compared to placebo. Median percent reduction in weekly seizure frequency was 29.3% (95% CI: 18.8, 41.9) and 39.6% (95% CI: 35.0, 48.7) for the everolimus LT and HT arms, respectively, compared with 14.9% (95% CI: 0.1, 21.7) for the placebo arm. The magnitude of effect as measured by both endpoints was considered clinically relevant, in particular taking into consideration that the study population was highly refractory with a high baseline seizure frequency and several previous failed AED regimens.

Long-term efficacy:

Reduction in seizure frequency was sustained over an evaluation period of approximately 2 years, during which all patients received everolimus. Based on a sensitivity analysis considering patients who prematurely discontinued everolimus as non-responders, response rates of 38.4% (95% CI: 33.4, 43.7) and 44.4% (95% CI: 38.2, 50.7) were observed after 1 and 2 years of exposure to everolimus, respectively.

Subgroup analyses by age showed higher response rates and increased reductions in seizure frequency for both everolimus treatment groups relative to placebo for all age categories (<6 years, 6 to <12 years, 12 to <18 years, and ≥ 18 years). Seizure frequency at the end of the core phase appeared markedly reduced within the lowest age category (2-5 years). Further analyses within the 2-5 year age category showed that a reasonable proportion of subjects was actually 2 years and 3 years old.

Study M2304 was used to build the popPK and popPD model as well as the linear mixed model, which were developed in order to predict the short-term efficacy and long-term efficacy, respectively of everolimus in the target population aged 6 months to below 24 months of age.

Modelling and simulation-based predictions of efficacy in target population

Predictions of short-term efficacy:

Reduction in seizure frequency (SF)

The popPD model predicted a substantial reduction in SF among paediatric patients at the predicted Cmin. The median predicted percentage reduction in SF was at least 64.2% (5th quantile; 95th quantile: 46.1%; 74.9%) at 24 weeks from the start of everolimus treatment, which was found for patients aged 22 months at the start of treatment. The predicted highest reduction in SF was 77.8% (5th quantile; 95th quantile: 60.6%; 87.6%), at 24 weeks from the start of everolimus treatment, which was found for patients aged 6 months at the start of treatment.

Percentage responders

The predicted median responder rate at the predicted 24-week Cmin was at least 57.5% (5th quantile; 95th quantile: 52%; 64%) and was found for patients who started everolimus at 22 months. The

predicted highest responder rate was 67.5% (5th quantile; 95th quantile: 61.5%; 72.5%) at 24 weeks and found for patients who started everolimus at 6 months of age.

Predictions of long-term efficacy:

Based on the long-term model-based analysis, the reduction in SF observed in study M2304 was 21.39% (95% confidence interval [CI]: 13.30-28.74) for a 2-fold increase in time-normalized Cmin. Every additional 12 weeks of exposure to everolimus was predicted to have a modest, but significant effect on SF, resulting in a further decrease of SF by 5.64% (95% CI: 3.54-7.70) per period. Additionally, a 0.5-fold reduction in baseline SF was predicted to reduce SF by 49.41% (95% CI: 45.68-52.89).

The proposed dosing recommendations for the target population remain the same as those approved for children aged 2 to < 6 years of age:

Therapeutic drug monitoring to maintain Cmin within a target concentration range is recommended for patients with TSC seizures to accommodate for the wide range of body sizes among infants and adults and the co-administration of CYP3A4 iso-enzyme inducers.

The recommended target Cmin exposure range is 5 to 15 ng/mL, based on data of seizure response and overall safety observable across this range. The recommended starting doses for patients <6 years of age is 6 mg/m2 when administered without CYP3A4/PgP inducer and 9 mg/m2 when administered with CYP3A4/PgP inducer. In addition, a flexible titration dose scheme of 1 to 4 mg is also recommended, which could potentially reduce the dose titration steps to attain the Cmin within the target Cmin range.

2.4.1. Discussion on clinical efficacy

Assessment of paediatric data on clinical efficacy

No clinical studies evaluating efficacy of everolimus for treatment of POS in TSC patients aged 6 month to < 2 years are available. Efficacy in this indication is intended to be extrapolated from children above 2 years of age and adults (source population) to patients aged 6 months to 2 years (target population) via modelling and simulation exercises based on previously submitted TSC studies.

Everolimus has been approved for treatment of refractory TSC associated POS in patients aged ≥ 2 years based on one pivotal study (M2304), which was now used to predict efficacy in the target population. The predicted (short-term) median reductions in seizure frequency were in the range of 40-70% compared to the actual median reduction in frequency of 30% in the low trough and 40% in the high trough dose group resulting from study M2304. Results of the linear mixed effect models also predicted maintenance of effect. However, there are shortcomings of the modelling and simulation approach indicating that the current model is not fit for its purpose, which is detailed in section 2.3 of this report.

Justification of extrapolation

The Applicant claims that the common aetiology of TSC and targeted mechanism of action of everolimus support the extrapolation of data from patients aged ≥ 2 years to patients aged 6 months-<2 years.

This is agreed insofar, as the over-activated mTOR signalling may be considered the general underlying aetiology of TSC while the general mechanism of action of everolimus is exerted via selective mTOR inhibition. However, besides pathological changes in brain tissue (such as cortical tubers) which may cause seizures, the dysregulation of the mTOR pathway is also considered to be directly implicated in the pathogenesis of epilepsy in TSC. Likewise, the exact mechanism of antiepileptic action of everolimus is not yet clear, and both, a reduction in pathological changes in brain tissue (which has been shown with

regard to SEGA) as well as direct reduction of hyper-excitability/seizure activity by inhibiting the hyperactive mTOR signalling may play a role.

However, structural brain lesions as epileptogenic foci may change with age, e.g. SEGA, which may lead to increase in seizure frequency or occurrence of new seizures, slowly arise over time during the first two decades of life.

It is currently unclear to what extent pathophysiology (POS aetiology) and mode of action may differ dependent on age and to what extent these factors may modify efficacy of everolimus between source and target population.

Further, two major assumptions underlie the bridging concept, i.e. that source and target population are similar with regard to:

1) the frequency, type and severity of (POS) seizures (including only rare emergency of new seizure types) and

2) a similar and stable concomitant AED treatment regime.

The validity of these assumptions is questioned.

Extrapolability of the exposure-response relationship in the approved TSC seizure indication from patients aged ≥ 2 years to patients aged 6 months to < 2 years is currently not adequately justified.

The Applicant finally agreed not to amend the currently approved indication but to update information relevant to the paediatric population in sections 4.2, 5.1 and 5.2 of the SmPC.

2.4.2. Conclusions on the clinical efficacy

Efficacy of everolimus in the treatment of refractory TSC associated POS in patients aged 6 months to < 2 years can at present not be concluded as extrapolation of the exposure-response relationship in the approved TSC seizure indication from patients aged ≥ 2 years to patients aged 6 months to < 2 years is not adequately justified. As a result, the Applicant agreed not to amend the currently approved indication but to update information relevant to the paediatric population in sections 4.2, 5.1 and 5.2 of the SmPC.

2.5. Clinical safety

Introduction

No new CSR has been submitted within this procedure.

Safety data in the target population (6 months to 2 years of age) are derived from the Novartis global safety database (ARGUS), including cases from previously conducted studies within TSC-related indications, and from literature articles.

Patient exposure

Definitions of 'key safety population' and evaluations performed

The target safety population for the purpose of the CO (explicitly the 'CO in patients 6 months to 2 years of age with refractory seizures associated with tuberous sclerosis complex (TSC)') are the patients between 6 months to <2 years of age (referred to thereafter as 'Target age group'), for the adjunctive treatment of POS with or without secondary generalization, associated with TSC (oncology patients were

not included in this study). Since no specific study is available, a search was conducted in the ARGUS safety database and a comparison of safety data was made between the target age group and the closest age group, i.e., children in the age group of 2 to <12 year-old (referred to thereafter as the 'Reference age group'). The age range of 2 to <12 year-old was used to get sufficient data as opposed to a narrower age range (e.g. 2 to 6 year-old) and to have comparable patients in terms of safety (which might not be the case for children older than 12 year-old).

Only children treated for TSC were included in both groups. No additional filtering on POS status was done since it was not systematically reported and only 4 patients in the target age group had an indication of TSC related seizures. Except seizure-related events, it is not expected that everolimus safety profile would be different in TSC patients with POS compared to those without POS.

The following sources have been used:

- Individual Case Safety Reports (ARGUS)
- Published scientific literature
- Official safety database (World Health Organization and AERS)

ARGUS was searched based on the patient's reported age or age group without any restriction in preferred terms. MedDRA version 22.0 was used for this search.

Exposure (in the 'key safety population')

Sales data for specific age groups was not available and hence the drug exposure could not be calculated for the target or the reference age groups. The estimated cumulative post-marketing (non-clinical trial) exposure values in patient years (PTY) is 23,522. This is the total patient exposure in TSC setting till date from post marketing experience across all age groups (cutoff date 31-Mar-2019). The available clinical trial exposure data in the paediatric age group is presented below:

Table 5-1 Cumulative exposure to everolimus in interventional clinical studies in the tuberous sclerosis complex setting stratified by age and sex (Safety set)

Gender	Age-group	*Double-blind everolimus N=404		*Double-blind placebo N=197		**Overall everolimus (Long-term evaluation) N=612	
		Subjects N (%)	PTY	Subjects N (%)	PTY	Subjects N (%)	PTY
Female	< one year	0	0	0	0	0	0
	≥ one year to < two years	3 (1.5)	3.4	4 (3.8)	3.3	3 (1.0)	13.0
	≥ two years to < three years	8 (4.0)	3.2	3 (2.9)	1.3	10 (3.3)	26.1
	≥ three years to < 12 years	80 (40.2)	41.5	38 (36.2)	19.2	122 (40.1)	333.8
Male	< one year	0	0	2 (2.2)	1.6	0	0
	≥ one year to < two years	5 (2.4)	5.3	1 (1.1)	0.3	7 (2.3)	22.8
	≥ two years to < three years	13 (6.3)	8.9	7 (7.6)	2.4	18 (5.8)	51.6
	≥ three years to < 12 years	89 (43.4)	41.5	39 (42.4)	15.0	136 (44.2)	374.9
Male and Female	≥ three years to < 12 years	169 (41.8)	83.0	77 (39.1)	34.1	258 (42.2)	709

PTY: Patient-Treatment-Years. PTY is the sum of each subject's treatment exposure in years. Data from following trials are included in the double-blind phase (M2301, M2302, and M2304) and the following in the overall analysis (M2301, M2302, M2304, and C2485).

* Double-blind phase: Subjects receiving everolimus or placebo during the double-blind treatment phase.

** Long-term evaluation phase: Subjects receiving everolimus during double-blind and/or open-label phases.

Adverse events

A cumulative search of ARGUS was conducted with a cutoff date of 12-Apr-2019, for adverse events with everolimus use in the target and reference age groups in the TSC indication.

The ARGUS search retrieved 1,314 cases with 4,809 events. The distribution of these cases between the two age groups is detailed in Table 5-2.

Table 5-2 Age distribution of patients with AEs

Age	Number of cases	Number of events	Serious events
Target age group (6 months to < 2 years)#	86	278	106

Reference age group (2 years to <12years)	1228	4531	1598

9 cases were reported as Neonates (0-1 Y) and another 9 cases were reported as Infants (1-2 Y) without any age; these 18 cases are accounted for in the target age group in the table.

AEs reported in both the target and reference age groups by system organ class (SOC) as well as the reporting ratios are summarized in Table 5-3 and presented visually in Figure 5-1. All cases are in the TSC indication.

Reporting ratios (RR) are defined as the number of events reported for the PT divided by the total number of events reported for the age group. The proportional reporting ratios (PRR) correspond to the RR for the target population divided by the RR for the reference population.

Table 5-3 Reporting ratios by SOC for age groups 6 months to less than 2 years and 2 to less than 12 years of age

SOC	Target (≥ 6m to <2y) Events (n)	Target (≥ 6m to <2y) RR (a%)	Reference (≥2 to <12y) Events (n)	Reference (≥2 to <12y) RR (b%)	PRR (a/b)
Blood and lymphatic system disorders	1	0.36%	30	0.66%	0.54
Cardiac disorders	**2**	**0.72%**	**14**	**0.31%**	**2.33**
Congenital, familial and genetic disorders	0	0.00%	3	0.07%	0.00
Ear and labyrinth disorders	0	0.00%	16	0.35%	0.00
Eye disorders	0	0.00%	30	0.66%	0.00
Gastrointestinal disorders	34	12.23%	713	15.74%	0.78
General disorders and administration site conditions	37	13.31%	510	11.26%	1.18
Hepatobiliary disorders	**1**	**0.36%**	**7**	**0.15%**	**2.33**
Immune system disorders	1	0.36%	26	0.57%	0.63
Infections and infestations	66	23.74%	877	19.36%	1.23
Injury, poisoning and procedural complications	**30**	**10.79%**	**189**	**4.17%**	**2.59**
Investigations	27	9.71%	417	9.20%	1.06
Metabolism and nutrition disorders	13	4.68%	139	3.07%	1.52
Musculoskeletal and connective tissue disorders	1	0.36%	47	1.04%	0.35
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0.36%	81	1.79%	0.20
Nervous system disorders	35	12.59%	536	11.83%	1.06
Psychiatric disorders	4	1.44%	281	6.20%	0.23
Renal and urinary disorders	1	0.36%	26	0.57%	0.63
Reproductive system and breast disorders	0	0.00%	14	0.31%	0.00
Respiratory, thoracic and mediastinal disorders	21	7.55%	360	7.95%	0.95
Skin and subcutaneous tissue disorders	3	1.08%	187	4.13%	0.26
Social circumstances	0	0.00%	1	0.02%	0.00
Vascular disorders	0	0.00%	27	0.60%	0.00
Grand total	**278**		**4531**		

RR = n / Grand total %
PRR = a/b
SOCs in bold occurred at a PRR above 2.

The most frequently reported preferred terms (PTs) in the target and reference age groups are presented in Table 5-4 below.

Table 5-4 Most frequently reported PTs (3 occurrences or more) in children 6 months to less than 2 years old and 2 to less than 12 years of age

PTs	Target age group (≥6m to <2y) Events (n)	RR (a%)	Reference age group (≥2 to <12y) Events (n)	RR (b%)	PRR (a/b)
Pyrexia	17	6.12%	223	4.92%	1.24
Seizure	16	5.76%	195	4.30%	1.34
Pneumonia	12	4.32%	116	2.56%	1.69
Stomatitis	12	4.32%	189	4.17%	1.03
Product use issue	**11**	**3.96%**	**16**	**0.35%**	**11.21**
Diarrhoea	10	3.60%	88	1.94%	1.85
Product use in unapproved indication	**10**	**3.60%**	**17**	**0.38%**	**9.59**
Malaise	8	2.88%	71	1.57%	1.84
Cough	7	2.52%	108	2.38%	1.06
Nasopharyngitis	6	2.16%	85	1.88%	1.15
Blood triglycerides increased	**4**	**1.44%**	**16**	**0.35%**	**4.07**
Decreased appetite	4	1.44%	37	0.82%	1.76
Drug level increased	4	1.44%	34	0.75%	1.92
Infection	**4**	**1.44%**	**12**	**0.26%**	**5.43**
Mouth ulceration	4	1.44%	63	1.39%	1.03
Off label use	**4**	**1.44%**	**7**	**0.15%**	**9.31**
Otitis media	**4**	**1.44%**	**11**	**0.24%**	**5.93**
Rhinorrhoea	4	1.44%	41	0.90%	1.59
Drug ineffective	3	1.08%	12	0.26%	4.07
Drug interaction	**3**	**1.08%**	**6**	**0.13%**	**8.15**
Epilepsy	**3**	**1.08%**	**23**	**0.51%**	**2.13**
Focal dyscognitive seizures	**3**	**1.08%**	**6**	**0.13%**	**8.15**
Hypertriglyceridaemia	**3**	**1.08%**	**8**	**0.18%**	**6.11**
Influenza	3	1.08%	44	0.97%	1.11
Pharyngitis	**3**	**1.08%**	**12**	**0.26%**	**4.07**
Respiratory tract infection	3	1.08%	13	0.29%	3.76
Viral infection	3	1.08%	31	0.68%	1.58
Vomiting	3	1.08%	93	2.05%	0.53
Wrong technique in product usage process	3	1.08%	24	0.53%	2.04
Grand Total*	**278**		**4531**		

*Grand total includes all reported PTs (including those reported only once or twice)
RR = n / Grand total %
PRR = a/b

The 278 events reported in the target age group, 92 (including 53 serious) were assessed as related to everolimus therapy by either the reporter or the MAH. Out of the 4531 events reported in the reference group, 1503 (including 1038 serious) were assessed as related to everolimus therapy by either the reporter or the MAH.

Serious adverse event/deaths/other significant events

A comparison of serious and non-serious cases does not show remarkable differences in terms of PRR between the target and reference age groups (Table 5-5).

The single fatal case in the target age group was a one-year old male child who died 3 days after initiation of everolimus treatment. At initiation of everolimus, the patient's neurological condition was very compromised including complete paralysis of the pharyngeal region, complicated with an inhalation pneumonitis, disturbances of consciousness with agitation, stupor, obnubilation, increase of left facial paralysis, absence of communication and obvious neurovegetative disorders (episodes of tachycardia, multifactorial fever). The subject died three days after initiation of everolimus, the cause of death according to death certificate was disease progression. No causality was suspected to everolimus treatment by the reporter or by the MAH. The cause of death in the 17 cases in reference group were reported as glioma (n=3), malignant neoplasm progression (3), general physical health deterioration (2), neoplasm progression (2), sudden unexplained death in epilepsy (2), respiratory distress (1), pneumonia (1), dyspnoea (1), disease progression (1), death (1), neurological decompensation (1), brain oedema(1), pneumonia aspiration (1), seizure (1),respiratory tract congestion (1), somnolence (1), depressed level of consciousness (1), cardio-respiratory arrest, syncope (1), asphyxia (1).

Table 5-5 Seriousness of events by age group

Event seriousness	Target (≥6m to <2y)		Reference (≥2 to <12y)	
	Events (n)	%	Events (n)	%
Not serious	172	61.9%	2933	64.7%
Serious	106	38.1%	1598	35.3%
Grand Total	**278**		**4531**	

Table 5-6 Case outcome by age group

	Target (≥6m to <2y)		Reference (≥2 to <12y)	
Case Outcome	Events (n)	%	Events (n)	%
Complete Recovery	28	32.6%	452	36.8%
Condition Improving	5	5.8%	118	9.6%
Condition Unchanged	11	12.8 %	201	16.4%
Recovered with Sequelae	0	0.00%	10	0.8%
Condition Deteriorated	0	0.00%	10	0.8%
Fatal/Death	1	1.2%	17	1.4%
Not Reported	41	47.7%	420	34.2%
Grand Total	**86**		**1228**	

Post marketing experience

The analyses based on the ARGUS Individual Case Safety Reports are considered as post-marketing experience but presented in the previous sections.

In addition to the analysis of the ARGUS data the MAH reports on post marketing experiences as follows:

Global external data and literature reports

Literature reports are in line with the ARGUS-reported data, and overall indicate that everolimus is well-tolerated.

In FDA AERS and WHO Vigibase databases as of 27-May-2019 in the age group of 0-23 months, the events with higher disproportionality scores (EB05 more than equal to 2) were similar to those reported in other age population (majority of these events are also listed for everolimus). All of these cases are from patients treated with everolimus.

In two separate studies, infants between 0 to 2 years of age were treated with everolimus for TSC, SEGA, refractory epilepsy, or related syndromes (Saffari et al 2019 and Krueger et al 2018). This included a total of 62 patients in the target age group. In both studies, most of the AEs were grade 1 or 2 in severity. Grade 3 AEs were reported in one study (7/45) (Krueger et al 2018); none of the studies reported any grade 4 or 5 (disability/death) events. Nine (out of 45) patients in one study discontinued due to AEs. Taken overall, the most common AEs in both studies were infections (or recurrent infections). This is similar to the observations from Novartis databases, which also showed that infections and infestations were the most frequently observed SOCs in the target population (Saffari et al 2019, Krueger et al 2018).

Two other studies in infants less than 12 months of age indicate similar results. Five patients received everolimus for SEGA and 4 patients for TSC-associated West Syndrome. Most of the AEs in both studies were low grade in severity (Samueli et al 2018, Kuki et al 2018). Grade 4 events (extensive impetigo contagiosa and recurrent pharyngitis) were reported in one study, that resolved after dose interruption (Samueli et al 2018).

2.5.1. Discussion on clinical safety

Safety in patients with TSC-associated refractory seizures is well-characterized, in paediatric patients 2 years of age and above.

Overall, no major difference in terms of reporting ratios emerges from the presented comparison. The high PRR (>2) for cardiac disorders (2 events of "minimal cardiac effusion" both in a context of viral infection), and hepato-biliary disorders (1 event) is mainly due to the low number of events in the target group; for injury, poisoning and procedural complications, 10 events of product use in unapproved indication and 4 of off-label use were reported that account for the difference in PRR (if these 14 events are removed from the computations, the PRR reduces from 2.54 to 1.35 (5.65%/4.18%)).

The overall profile of AEs by PT was similar in both age groups (6 months to <2 years and >2 years).

PTs with a higher reporting ratio in the target age group (more than twice that of the reference age group) are discussed below:

- Otitis media, infection, pharyngitis, respiratory tract infection that can be explained by a higher sensitivity to infections in this age group
- Focal dyscognitive seizures and epilepsy reflect the underlying TSC. However, the absolute number of cases are low in the target age group; therefore, it is not possible to draw any conclusions.
- Hypertriglyceridemia and increased blood triglycerides are listed events that were all non-serious except for one case (medically significant as per reporter) in a 22-months old patient with a family history of hypertriglyceridemia. However, the absolute number of cases are low in the target age group; therefore, it is not possible to draw any conclusions.
- Three cases of drug interaction were reported: in one case of interaction with oxcarbazepine, everolimus level fluctuations were associated with recurrence of seizures, in another case of interaction with phenytoin and phenobarbital, no clinical events were reported and in the last case of interaction with voriconazole non-serious liver disorder was reported concomitantly with the interaction and abated after everolimus blood levels had decreased following dose adjustment. Three non-serious cases of drug ineffective were also reported for the target age group.

Note: 'Product use issue', 'Product use in unapproved indication', 'Wrong technique in product usage process' and 'Off label use' were reported with a higher reporting ratio in the target age group relative to the reference age group. This observation could suggest various situations, including the use in a population for which everolimus is not approved.

The patients included in the safety database could have received different doses of everolimus. However, the impact is expected to be minimal, considering that treatment with everolimus is titrated to target trough plasma levels between 5 to 15 ng/mL.

A review of the individual case safety reports from the Novartis Safety database in the target age group of children between 6 months and 2 years of age did not present any potential new safety signal. The analysis neither presented a pattern of data that could indicate a change in characteristic of a known safety issue, nor warranted a follow up on specific safety topics. With the limited post-marketing data available in the target age group for review, there was no safety information that could impact the safety profile of everolimus for this population. Based on post marketing safety data, evaluation of the safety profile of everolimus in the target age group appears to be consistent with that of the population for which everolimus is currently approved.

The safety experiences with everolimus presented do not refer to the treatment of seizurers in children with TSC below the age of 2 years (There were no cases reported in Novartis safety database where the indication for use of everolimus was seizure associated with TSC in the target age group of 6 months – 2 years.).

In conclusion, the presented analysis could not show any meaningful difference between the target and reference age groups with respect to the nature of reported events, their seriousness, or their outcome.

In addition, section 4.8 of the current SmPC is already pooling data across different TSC indications (i.e. pivotal phase II and III trials). These data are limited to patients **older than 1 year** of age. In essence, considering that from a safety perspective pooling of data of patients with AML, POS and SEGA is considered acceptable by CHMP, the remaining safety question not addressed by section 4.8 of the SmPC, and by the Novartis Safety database in the target age group of children between 6 months and 2 years, is the safety of everolimus in the age 6 months to 1 year (for which no pre- and post-marketing data are reported). However, the scope of this application was revised and only information relevant to the paediatric population in sections 4.2, 5.1 and 5.2 of the SmPC was updated.

2.5.2. Conclusions on clinical safety

The CHMP considers safety in paediatric patients with TSC 1 years of age and above to be well-characterized. An extrapolation of clinical safety in TSC-associated refractory seizures to TSC-associated SEGA (or TSC in more general) is considered meaningful.

There are no safety data available to support the use of everolimus in the age range **6 months to 1 year**. The Applicant finally agreed not to amend the currently approved indication but proposed to update relevant information in sections 4.2, 5.1 and 5.2 of the SmPC.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Update of the Product information

As a consequence of this variation, sections 4.2, 5.1 and 5.2 of the SmPC have been updated:

Section 4.2:

The safety, efficacy and pharmacokinetic profile of Votubia has not been established in children below the age of 2 years with TSC and refractory seizures ~~have not been established~~. Currently available data are described in section 5.2, but no recommendation on a posology can be made. ~~No data are available (see sections 5.1 and 5.2).~~

Section 5.1:

~~The European Medicines Agency has deferred the obligation to submit the results of studies with Votubia in one or more subsets of the paediatric population in refractory epilepsy associated with tuberous sclerosis complex (see section 4.2 for information on paediatric use).~~ The marketing authorisation holder has completed the Paediatric Investigation Plan for Votubia for refractory seizures associated with TSC. This summary of product characteristics has been updated to include the results of studies with Votubia in the paediatric population (see section 5.2).

Section 5.2:

In patients with TSC and refractory seizures Votubia concentrations were investigated in 9 patients in the age between 1 and<2 years. Doses of 6 mg/m2 (absolute doses range 1-5 mg) were administered and resulted in minimal concentrations between 2 and 10 ng/ml (median of 5 ng/mL; total of >50 measurements). No data are available in patients with TSC-seizures below the age of 1 year.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s).

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This variation was submitted in order to modify the approved therapeutic indication, adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalisation, are associated with tuberous sclerosis complex, to include the new population of patients from 6 months to less than 2 years of age.

3.1.2. Available therapies and unmet medical need

Seizures associated with TSC are treated with antiepileptic drugs (AEDs) or methods such as epilepsy surgery, vagal nerve stimulator or ketogenic diet (Jobst 2009; Wong 2010). Other than for infantile spasms in TSC for which vigabatrin is usually recommended as first line treatment, there is little evidence to guide effective anticonvulsant treatment. The published literature suggests that TSC-associated POS may respond to one or several AEDs approved for the treatment of POS, e.g. topiramate, lamotrigine, levetiracetam, oxcarbazepine, and clobazam. The prevalence of medically refractory epilepsy in TSC even

with adequate trials of currently available anticonvulsant medications has been reported as high at approximately 60%.

3.1.3. Main clinical studies

No clinical studies evaluating efficacy of everolimus for treatment of POS in TSC patients aged 6 month to < 2 years were submitted. This application is based on a physiologically based pharmacokinetic (PBPK) model and a population pharmacokinetic model (popPK).

3.2. Favourable effects

The Applicant intended to extrapolate efficacy in this indication from children above 2 years of age and adults (source population) to patients aged 6 months to 2 years (target population) via modelling and simulation exercises based on previously submitted TSC studies. Everolimus has been approved for treatment of refractory TSC associated POS in patients aged ≥ 2 years based on one pivotal study (M2304), which was intended to be used to predict efficacy in the target population. The predicted (short-term) median reductions in seizure frequency were in the range of 40-70% compared to the actual median reduction in frequency of 30% in the low trough and 40% in the high trough dose group resulting from study M2304. Results of the linear mixed effect models also predicted maintenance of effect. The exposure-response model is based on exposure parameters derived from the PBPK model.

3.3. Uncertainties and limitations about favourable effects

Extrapolation of exposure-response relationship of everolimus in the TSC-associated POS indication from patients aged ≥ 2 years (source population) down to patients aged 6 months of age (target population) was not convincingly justified by the Applicant.

There finally remains uncertainty as to what extent brain maturation impacts the disease and the treatment response in children younger than 2 years of age. Taking further into account that everolimus is not a "standard" AED but a substance considered to affect epileptogenesis, generation of clinical data in the target population in order to provide reassurance that a clinically meaningful treatment response with regard to TSC associated POS can be achieved in children below 2 years of age was considered necessary. The Applicant argued that the conduct of a confirmatory epilepsy study in TSC subjects of the targeted age range is challenging and would not be possible. This is acknowledged. However, general infeasibility to generate at least some clinical treatment data on seizure frequency in TSC subjects below the age of two years is not considered plausible.

Further, there are two major assumptions underlying the bridging concept, i.e., that source and target population are similar with regard to 1st) the frequency, type and severity of (POS) seizures (including only rare emergence of new seizure types) and 2nd) a similar and stable concomitant AED treatment regime.

Regarding the 1st assumption, little information regarding POS seizure characteristics in the target population is available. There is some indication though, that seizure frequency in the target population may be higher compared to the source population. Within the source population, POS frequency was higher with younger age in study M2304 and baseline seizure frequency was a statistically significant factor in the exposure-efficacy models of study M2304. Further, there are age-related differences regarding the overall seizure characteristics, as the age related seizure type of infantile spasms often co-occurs or may be even the predominant seizure type in the target population, particularly in the youngest age group below 1 year of age.

A discussion including respective evaluations of M2304 study results, in how far potential differences with regard to subtype, frequency and severity of POS could be expected to not essentially influence efficacy of everolimus in the target population has not been provided.

Regarding the 2nd assumption, the differences in the concomitant AED regimens appear mainly related to the more frequent use of vigabatrin and ACTH/corticosteroids in TSC subjects below < 2 years of age. From an efficacy point of view, there are remaining uncertainties regarding a potential pharmacokinetic interaction of everolimus with corticosteroids and no data on the impact of concomitant use on seizure reduction is available. Furthermore, no data on concomitant use of everolimus and vigabatrin has been presented; however, a pharmacokinetic interaction with vigabatrin is considered unlikely.

3.4. Unfavourable effects

Unfavourable effects, based on CSRs, of everolimus in patients **age 1 to 2 years** are, although limited, entirely described in section 4.8 of the SmPC of the product. No new safety data deriving from CSRs have been generated for the scope of this variation II/61. The post-marketing safety data made available within this procedure do not add relevant new information for the mentioned age group.

3.5. Uncertainties and limitations about unfavourable effects

For the age group 6 months to 1 year, no safety information at all is available. In addition, no safety data (including post-marketing data) for the age group 1 to 2 years are available for the treatment of (TSC associated) seizures with everolimus.

Extrapolation of safety data from patients ≥ 2 years of age to the delicate age group of infants (up to the first year of life) in the absence of any PK or safety data in the latter is considered problematic.

3.6. Effects Table

No new clinical data were submitted.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy of everolimus in the treatment of refractory TSC associated POS in patients aged 6 months to < 2 years can at present not be concluded as extrapolation of the exposure-response relationship in the approved TSC seizure indication from patients aged ≥ 2 years to patients aged 6 months to < 2 years has not been adequately justified. Additional evaluation, in how far differences between source and target population with regard to the two major assumptions underlying the bridging concept may modify the predicted treatment effect was not provided. Further, the Applicant did not make a proposal for a clinical study in order to provide reassurance that a clinically meaningful treatment response can be achieved in patients < 2years with regard to TSC associated POS.

Safety data in the treatment of TSC associated with AML, POS, and/or SEGA can reasonably be pooled, which was already concluded by the CHMP and is implemented in section 4.8 of the SmPC accordingly.

No (pre- or post-marketing) safety data in the group of patients younger than 1 year are available for the overall, pooled safety TSC population. In the specific POS TSC population, the MAH is no longer claiming a positive B/R in children younger than 2 years of age.

3.7.2. Balance of benefits and risks

Efficacy of everolimus in the treatment of refractory TSC associated POS in patients aged 6 months to < 2 years cannot be concluded currently. Safety data in patients with TSC aged > 1 year are available. In the overall TSC population, safety of everolimus can be concluded for this age group based on the data presented (and reported in the SmPC). However, in the specific POS TSC population, there are no safety data for children below the age of 2. Therefore, the balance of benefits and risks in the proposed age group 6 months to < 2 years can currently not be assessed in TSC patients treated for seizures.

Because of the CHMP's concern with the provided extrapolation approach, the Applicant agreed not to amend the currently approved TSC-seizure indication.

3.7.3. Additional considerations on the benefit-risk balance

As the extrapolation of exposure-response from source to target population has not been sufficiently justified, no information regarding the reduction in TSC associated refractory seizure frequency as predicted by the modelling was included in section 5.1 of the SmPC. Further, the PBPK model is not considered appropriate to predict exposure outside the investigated range. Nevertheless, addition of relevant information on concentration data generated in children aged 1-2 years to section 5.2 of the SmPC was agreed.

3.8. Conclusions

The overall B/R of Votubia is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIA

Update of sections 4.2, 5.1, and 5.2 of the SmPC based on results from a modelling and simulation study of patients from 6 months to less than 2 years of age whose refractory partial-onset seizures, with or without secondary generalisation, are associated with tuberous sclerosis complex. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.1.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Labelling.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II, and IIIA are

recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0316/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-0061'