NOVARTIS

Oncology Region Europe

RAD001/Everolimus/Votubia®

Non-interventional Study Protocol CRAD001MIC03

An international disease registry collecting data on manifestations, interventions and outcomes in patients with tuberous sclerosis complex -TOSCA

Authors: [redacted]

Document type:	Amended Protocol Version
Version number:	03 (Clean)
PASS Study	No
Study phase:	Not Applicable
Document status	Final
Release date:	30 July 2014

Property of Novartis
Confidential
May not be used, divulged, published or otherwise disclosed
without the consent of Novartis

Marketing authorization holder(s)

Marketing authorization holder(s)	Novartis A.G. Lichtstrasse 35, 4056 Basel, Switzerland
MAH contact person	[redacted]

1 Table of contents

List of tables

List of figures

2 List of abbreviations

AE	Adverse Event
AF	Facial Angiofibroma
AML	Angiomyolipoma
ATC	Anatomical Therapeutic Chemical
BOI	Burden of illness
CatPCA	Categorical Principal Component Analysis
CFR	Code of Federal regulations
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTH	Clinical Trial Head
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ESRD	End-stage renal disease
FA	Factor analysis
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practices
ICF	Informed Consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IPSP	Individual Patient Supply Program
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LAM	Lymphangiomyomatosis
MRI	Magnetic resonance imaging
mTOR	Mammalian Target of Rapamycin
PAG	Patient Association Group
PASS	Post-Authorization Safety Study
PCA	Principal Component Analysis
PHI	Protected health information
PRO	Patient-reported Outcomes
QOL	Quality of life
REB	Research Ethics Board
RG	Research Group
RP	Research Project
SAB	Scientific Advisory Board
SAE	Serious Adverse Event
SEGA	Subependymal giant cell astrocytoma
SEN	Subependymal nodules
SmPC	Summary of Product Characteristics
SPSS	Statistical package for the social sciences (SPSS)
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TAND	TSC-associated neuropsychiatric disorders
TDM	Therapeutic Drug Monitoring
TOSCA	Tuberous Sclerosis Registry to increased disease awareness

TSC	Tuberous Sclerosis Complex
WC	Working Committee
WHO	World Health Organization

3 Responsible Parties

Please refer to Section 14.1 in the TOSCA PASS sub-study.

4 Abstract

Title	An International Disease Registry Collecting Data on Manifestations, Interventions and Outcomes in Patients with Tuberous Sclerosis Complex – TOSCA
Version and Date	03 amended protocol, 30July 2014
Name and affiliation of main author	[redacted]
Rationale and background	Tuberous Sclerosis Complex (TSC) is an autosomal dominant genetic disorder caused by inactivating mutations in the tuberous sclerosis complex tumor suppressor genes, TSC1 or TSC2, affecting tuberin and hamartin respectively. The results of a second somatic mutation in the heterozygous background include benign, highly vascular, hamartomatous growths. Lesions occur in the brain, kidneys, heart, liver, lungs and skin, and phenotypically can manifest with renal and or pulmonary complications, autism, mental retardation and epilepsy (Gomez et al 1999; Astrinidis and Henske 2005; Inoki et al 2005; Kwiatkowski and Manning 2005). Measures of childhood prevalence range from 1 in 6,800 to 1 in 17,300 but full ascertainment is difficult to achieve (Yates 2006). Brain lesions are the primary cause of morbidity and mortality in this disorder in childhood. After neurologic manifestations, renal lesions are the most common cause of morbidity and mortality in TSC (Franz 2004). There is common agreement that there are still gaps in understanding the course of TSC manifestations and their prognostic role, rare symptoms and co-morbidities, interventions, treatments and their outcomes, and quality of life. The registry described in this protocol will address many of these gaps by collecting data from patients across many countries worldwide that would not be sufficient if only collected from patients in an individual country. The data collected might influence and improve patient's treatment standards and flows. An additional purpose of this registry is to inform the research in TSC. Following the EMA's request (EMEA/H/C/002311/II/0004), data on the long-term safety of the prescribed treatment with Votubia® (everolimus) in the licensed indications will be collected in a TOSCA safety sub-study (Appendix 1) classified as Post-Authorization Safety Study (PASS) to characterize the important identified risks, potential risks (e.g. male infertility) and missing information listed in the Votubia® Risk Management Plan (RMP Version 9/8,November 2013).
Research question and objectives	**Registry objectives:** The objectives of the registry are: • [redacted] **TOSCA PASS objectives:** • [redacted] Following the approval of Amendment 3, additional data on specific disease manifestation will be collected through the implementation of six research projects developed by the Research Groups (RG). Each research project will have specific objectives.
Study design	The TOSCA disease registry is designed to collect information on a large international cohort of patients with TSC. The TOSCA disease registry is structured to collect retrospectively and prospectively patient and disease information. General mandatory information on patient's background, including demographics, family, prenatal, vital signs and disease features are collected in the 'Core' section of the registry at baseline and updated yearly, if available.

	Additional and more detailed data related to specific disease manifestations will be collected in sub-sections (i.e. research projects) of the registry and will be updated yearly or according to the procedures described for each Research Project (Appendices 2-7). Retrospective and prospective data are therefore collected from both patient characteristics and disease specific information of any subjects enrolled in the registry. In this registry no clinical instrumental or laboratory assessments/interventions will be performed other than those required for disease management according to local best practice or required to monitor any treatment as per locally approved summary of product characteristics or if patient is taking part of an approved clinical study, if applicable. The only exception will be the patient reported outcome questionnaires to assess quality of life (QOL) and burden of illness (BOI) (Research Project 6) and the TAND checklist (Research Project 4). These sub-projects will be launched upon relevant IRB/EC and HA/CA approvals of the protocol amendment 3. Follow up patient's visits will be scheduled according to the standard practice of the site and to the treating physician's best judgment or as specified in the ongoing clinical studies. It is assumed that at least a disease assessment every 12 months in the context of regular follow up visits will be performed. Disease evaluation could be performed more frequently, if needed. Any valuable information collected at follow up visits will be recorded in the registry. For each patient enrolled in the registry a minimum of one yearly update (10 ± 2 month interval) is scheduled to ensure an ongoing data stream. Designated registry staff will enter the data into an electronic Case Report Forms (eCRFs) through a web-based internet system using fully validated software that conforms to regulatory requirements for electronic data capture. The initial enrollment period for the disease registry is anticipated to be about 24 months with a follow-up observation period of up to 5 years. Only for the pediatric patients included in the TOSCA PASS, the follow-up period will be extended until they reach Tanner stage V, if evaluated per local routine practice, or until age 16 for females or 17 for males, regardless of the end of trial therapy, in order to collect long term data on sexual maturation and fertility. Since the database is ongoing for up to 15 years (only for the data collection of the pediatric patients included in the TOSCA PASS until they reach Tanner stage V if evaluated per local routine practice, or until age 16 for females or 17 for males, regardless of the end of trial therapy), retrospective revisions/additions will be possible at any time as additional or corrective data emerges. The follow-up of initial and additional patients after the closure of the TOSCA PASS could be conducted by Novartis or possibly by a third party organization, including a non-profit organization. The TOSCA PASS is a non-interventional, multi-center post-authorization safety study conducted in [redacted]. Since the TOSCA PASS is a sub-study of the TOSCA disease registry the observation period of the patients for the long term safety will last until the closure of the TOSCA disease registry (up to 5 years for patients not included in the TOSCA PASS sub-study or with an age greater than 16 for females or 17 for males or at Tanner stage V, if evaluated per local routine practice, up to 15 years for the pediatric patients included in the TOSCA PASS sub-study). It is anticipated that 150 patients meeting eligibility criteria after informed consent signature will be enrolled in the safety sub-study from approximately 100 sites in more than 15 countries, in the European Union. In order to reach the target of 150 patients, the enrollment in the TOSCA registry will be extended over the initial enrollment of 24 months in countries participating to the TOSCA PASS sub-study. Follow up patient's visits will be scheduled according to the standard practice of the site and to the treating physician's best judgment or as specified in the ongoing clinical studies. It is assumed that at least a disease assessment every 3 months in the context of regular follow up visits will be performed. Disease evaluation could be performed more frequently, if needed. Any valuable information collected at follow up visits will be recorded in the registry. Data collected for the TOSCA PASS will be entered in the TOSCA database. Data to fulfill the objectives of the TOSCA registry will be collected for all TSC patients included in the TOSCA registry. In addition, long-term safety data of treatment with prescribed Votubia® in the licensed indications will be collected for

	patients participating to the TOSCA PASS sub-study to fulfill the objectives of the TOSCA PASS sub-study. The analyses for the TOSCA registry objectives like [redacted]
Population	**Registry population**: Male or female alive patients of any age with a diagnosis of TSC, with documented visit for the disease within 12 months or newly diagnosed. Registry participating physicians should obtain informed consent (ICF) signature (parental/guardian consent if applicable) to entitle enrollment in the TSC registry. **Inclusion/Exclusion criteria:** Patients eligible for inclusion in this registry have to meet all of the following criteria: 1. Patient with diagnosis of tuberous sclerosis complex 2. Male or female alive patients of any age 3. Patient with a documented visit for TSC within 12 months or newly diagnosed with TSC prior to agreement to participate in the registry by physician-patient ICF signature 4. Patient must sign ICF (parental/guardian consent, if applicable) before any data or information is provided into the registry Patients eligible for inclusion in this registry must not meet any of the following criteria: 1. According to registry participating physician's opinion the patient is an unlikely candidate to provide follow-up information e.g., for reasons of unavailability. 2. Patients currently participating in interventional Novartis sponsored clinical trials with everolimus in TSC. In case a patient already participating to TOSCA registry is enrolled in any interventional Novartis sponsored clinical trial in TSC or starts receiving everolimus through the Individual Patient Supply Program (IPSP), the patient's data collection in TOSCA will be put on hold until the discontinuation from the interventional clinical trial or IPSP in order to avoid any duplication of data collection. Patients previously treated with everolimus through the IPSP or patients enrolled in a Novartis sponsored Expanded Access Study and switched to prescribed Votubia® are eligible. **TOSCA PASS population**: Patients in the European Union participating in the TOSCA disease registry on treatment with Votubia® at the time of enrolment or patients who start treatment with Votubia® after enrolment in the TOSCA disease registry. Patient's signature (parental/guardian consent if applicable) of the informed consent specific for the TOSCA PASS must be obtained prior to enrollment in the TOSCA PASS. **TOSCA PASS Inclusion/Exclusion criteria:** Patients eligible for inclusion in this sub-study have to meet all of the following criteria: 1. Patients participating in the TOSCA disease registry 2. Patients on prescribed treatment with Votubia® in the licensed indications in the European Union 3. Patient must sign the TOSCA PASS ICF (parental/guardian consent, if applicable) before any data or information is provided into the safety sub-study No exclusion criteria other than the ones required for participation in the TOSCA disease registry
Variables	The outcome of interest for the TOSCA disease registry are: 1. [redacted] 2. [redacted] 3. [redacted] 4. [redacted] 5. [redacted]

	[redacted] 6. [redacted] e The Outcomes of interest for the TOSCA PASS are: 1. [redacted] 2. [redacted] 3. [redacted] 4. [redacted] **Safety related measurements:** The TOSCA PASS is non-interventional in nature and does not impose a therapy protocol, diagnostic/therapeutic interventions or a visit schedule. Available data from routine clinical management of the patients will be collected at patients' visits to their site. To maintain adequate data collection, the sites will be encouraged to provide any updated patient data at 3-monthly intervals.
Data sources	The data for this study will be retrieved from hospital discharge files, clinical records, electronic medical records, patients' questionnaires, ad hoc clinical databases. Sites enrolling patients in this study will record data on eCRF provided by Novartis (or designee) which will capture, check, store and analyze the data. CROs will follow their own internal Standard Operating Procedures (SOPs) that have been reviewed and approved by Novartis. Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.
Study size	**Number of patients:** The registry is open to all TSC patients and it is estimated that approximately 2000 patients meeting eligibility criteria after physician-patient informed consent signature to participate in the registry will be enrolled from roughly 250 sites in more than 30 countries worldwide. This enrollment estimate may vary and will be flexible since no formal sample size is required due to the descriptive nature of this registry and the lack of a specific hypothesis to be tested. **Number of TOSCA PASS patients:** It is anticipated that approximately 150 patients, will be enrolled in the TOSCA PASS from roughly 100 sites in about 15 countries in the European Union. The estimated sample size of at least 150 patients was chosen based on the expected Votubia® approval and availability in the participating countries. The actual sample size may differ as availability of Votubia® changes.
Data analysis	All patients enrolled in the registry will be considered in the analysis. Demographic and clinical parameters will be tabulated for the descriptive statistical analyses of relevant variables. Given the descriptive nature of this registry and the lack of a specific hypothesis to be tested, there is no formal sample size calculation. The first administrative interim analysis, planned when complete data collection for the baseline 'Core' data set for 100 patients are entered into the registry database will be aimed at evaluating feasibility and efficacy of data collection procedure. The subsequent analyses planned approximately every 12 months will be focused on registry aims. **TOSCA PASS**:The primary variable of the TOSCA PASS is the [redacted] The incidence of AEs and SAEs will be summarized by system organ class and preferred term using the MedDRA dictionary. Similar summaries will also be produced for treatment-related AEs and SAEs. These listings will cover both events

	that occur during the on-treatment and post-treatment period. Other variables are the following: • [redacted] • [redacted] • [redacted] Interim analyses are planned yearly until study end.
Milestones	Start of data collection: 10-Aug-2012 End of data collection for the patients included in the disease registry and for patients included in the TOSCA PASS who already reached Tanner stage V or age of 16 for females and 17 for males at the time of end of data collection: 10-Aug-2017 Study progress report(s): Yearly update Interim report(s) of study results, if applicable: Yearly update Final report results of patients included in the disease registry: December 2017. End of data collection for the pediatric patients included in the TOSCA PASS: 10-Aug-2027. Final report results of patients included in the TOSCA PASS: December 2027.

5 Amendment and updates

5.1 Amendment 3

Amendment Rationale

The study protocol has been primarily amended to allow the collection of additional data on specific disease manifestations through the implementation of six research projects developed by the Research Groups (RG).

Data of these research projects will be collected within the end of the collection of data in the TOSCA registry (i.e. August 2017).

The research projects implemented with this protocol amendment are:

1. **Research Project 1. Characterizing SEGA in TSC with respect to their pattern of growth, their impact on CSF circulation, their relation to neurologic and cognitive impairments and potential treatment options**
   - The objectives of the Research Project are to better study the [redacted]
   - Data on SEGA growth characteristics, signs and symptoms, imaging aspects, treatment, and histology will be collected.
   - This Research Project will be run in all countries involved in TOSCA and interested in participating to this Research Project.
2. **Research Project 2. Defining the risk factors in renal disease in TSC and the effect of treatment on prognosis**
   - The objective of the Research Project is to [redacted]
   - This Research Project will be run in all countries involved in TOSCA and interested in participating to this Research Project
3. **Research Project 3. Genotype/Phenotype correlations in TSC**
   - The main objective of this project is to [redacted]
   - In addition, [redacted]
   - Cases with intra-familial variability of the disease severity will be collected in order to develop future studies on modifier genes.
   - This Research Project will be run in all European countries involved in TOSCA and interested in participating to this Research Project.
4. **Research Project 4. Exploring the multidimensionality of TSC-Associated Neuropsychiatric Disorders (TAND)**
   - The administration of the TAND checklist is part of the clinical practice according to the 2012 international guidelines of TSC surveillance and management (Krueger DA, Northrup H, 2013).

- The main objective of the study is to [redacted] The identification of natural TAND clusters may be a very helpful first step towards prioritization of clinical concerns and support the generation of treatment guidelines for TAND. TAND cluster analysis may also generate [redacted]
- This Research Project will be run in all countries involved in TOSCA and interested in participating to this Research Project.

5. **Research Project 5. How TOSCA can help improve the knowledge of epilepsy in TSC**
   - This Research Project will explore in a large cohort the intimate characteristics of the epilepsy and its impact in patients from different ethnical and cultural backgrounds with TSC.
   - The objectives of the Research Project are to [redacted]
   - This Research Project will be run in all countries involved in TOSCA and interested in participating to this Research Project.
6. **Research Project 6. Quality of Life and Burden of Disease in TSC**
   - The objective of the Research Project is to [redacted]
   - Patients included in the Research Project will be asked to complete a questionnaire that includes:
     - One validated questionnaire of quality of life (EQ5D for adults; EQ5D proxy version 1 to be completed by caregivers for children or disabled patients),
     - One validated questionnaire of quality of life in epilepsy (Quality of Life in Epilepsy Inventory-31-Problems (QOLIE-31P) for adults; Quality of Life in Childhood Epilepsy (QOLCE) for children <10 years old to be completed by caregivers; Quality of Life in Epilepsy Inventory for Adolescents QOLIE-AD-48 to be completed by adolescents 11-17 years old)
     - Ancillary disease specific questions on the BOI (e.g., patient assistance requirements and support/rights, access to healthcare resources, sources of information, clinical trial experience, socio-economic and financial impact, genetic counselling, …)
   - The ancillary questions were developed in collaboration with the TSC patient associations through the patient representatives involved in the Research Project.
   - In addition, physicians will be requested to answer to questions on the BOI in the TOSCA registry.
   - This Research Project will be run in all European countries involved in TOSCA and interested in participating to this Research Project.

Additional modifications implemented with this amendment are:

- To adjust the skeleton of the protocol in order to align the structure with the Novartis non-interventional trial template.
- To amend the age until which pediatric patients are planned to be followed up from 15 for females and 16 for males to 16 for females and 17 for males to comply with EMA request (EMA/CHMP/59467/2014, 20 February 2014)
- To specify that the inclusion in the registry of patients eligible for the TOSCA PASS will continue over the initial enrollment of 24 months to reach 150 patients in the TOSCA PASS.
- To specify that when a patient already participating in the TOSCA registry is enrolled in a Novartis sponsored interventional trial in TSC or starts receiving everolimus through an Individual Patient Supply Program (IPSP), the patient's data collection in TOSCA will be put on hold until the discontinuation from the interventional clinical trial or IPSP in order to avoid any duplication of data collection.
- To update the safety information on everolimus (Votubia®), according to the Investigator's Brochure Edition No. 13
- To update the list of important identified and potential risks according to the current Afinitor/Votubia® Risk Management Plan V9.0/V8.0
- To specify that for patients <3 years of age treated with Votubia for SEGA the everolimus blood trough level should be assessed, at least 1 week after commencing treatment or any change of dose or pharmaceutical form. This is according to the current SmPC
- To update the version of the Scientific Advisory Board (SAB) and Working Committee (WC) charters currently in use.
- To clarify the members of the Operational Team
- To specify the process for transferring the Adverse Event information to Novartis
- To correct typographical and grammatical errors as well as protocol inconsistencies.

Changes to the protocol

Changes to the specific sections of the protocol are shown in the track changes version of the protocol using strike through red font errors for deletions, red (underline) for insertions.

Marketing authorization holder(s)

The marketing authorization holder section has been included to ensure alignment with the non-interventional trials study protocol template.

Synopsis

The synopsis has been deleted and replaced by an abstract to ensure alignment with the non-interventional trials study protocol template. All the changes implemented in the body of the protocol have been included in the abstract.

Section 1 and 2

The title of the section 1 has been changed from "Background" to "Rationale and Background" to ensure alignment with the non-interventional trials study protocol template.

The "Purpose and Rationale" section has been merged with the "Background" (Section 7) to ensure alignment with the non-interventional trials study protocol template.

The numbering of the sections and headings has been updated accordingly.

The 2012 International TSC guidelines have been added into the overview of the disease.

Section 3

The title of the section has been changed from "Objectives" to "Research Question and Objectives" to ensure alignment with the non-interventional trials study protocol template.

The numbering of the section and headings has been updated.

Table 3.1 has been updated with the current list of important identified and potential risks according to the Afinitor/Votubia® Risk Management Plan V9.0/V8.0. The numbering of this table has been changed from 3.1 to 8.1.

The section has been further modified to specify that additional data will be collected for specific disease manifestations and that each Research Project will have specific objectives.

Section 4

The study design section has been included in a new section entitled "Research Methods" (Section 9).

The numbering of the section and headings has been updated to ensure alignment with the non-interventional trials study protocol template.

Section 4.1 has been modified to specify that additional data on disease specific manifestations will be collected yearly or according to the procedures described for each Research Project and that the only exception in the routine clinical management of the disease will be the administration of the patient reported outcome questionnaires to assess quality of life (QOL) and burden of illness (BOI) (Research Project 6) and the TAND checklist (Research Project 4). These sub-projects will be launched upon relevant IRB/EC and HA/CA approvals of the protocol amendment 3.

The section has been changed to amend the age until which pediatric patients are planned to be followed up from 15 for females and 16 for males to 16 for females and 17 for males to comply with EMA request

Section 4.3 has been modified to specify that the enrollment for TOSCA PASS sub-study will continue until 150 patients are recruited in the sub-study.

Section 5

The title of the section has been changed from "Population and Setting" to "Setting" to ensure alignment with the non-interventional trials study protocol template.

The numbering of the section and headings has been updated to ensure alignment with the non-interventional trials study protocol template.

The Section 5.1 has been modified to specify that when a patient included in the TOSCA registry is enrolled in a Novartis sponsored interventional trial in TSC or starts receiving everolimus through the Individual Patient Supply Program (IPSP), the patient's data

collection in TOSCA will be put on hold until the discontinuation from the interventional clinical trial or IPSP in order to avoid any duplication of data collection.

"Variables" and "Study size" sections have been added in "Research Methods" (Section 9).The numbering of the Section 5.3 has been updated to ensure alignment with the non-interventional trials study protocol template.

Sections 6 and 7

The sections 6, 6.1 and 6.2 have been deleted in order to ensure alignment with the non-interventional trials study protocol template.

Sections 6.3.1, 7, 7.1, 7.1.1, 7.1.2, 7.2, 7.2.1, 7.3, 7.3.1 have been included in a new section entitled "Data collection schedule" (Section 9.5.1).

Section 7 has been modified to specify that the only exception in the routine clinical management of the disease will be the administration of the patient reported outcome questionnaires to assess quality of life (QOL) and burden of illness (BOI) (Research Project 6) and the TAND checklist (Research Project 4) and to specify that following the approval of Amendment 3 additional information on specific disease manifestations will be collected at baseline according to the research projects procedures.

Section 8

The safety monitoring and reporting section has been moved and re-numbered according to the non-interventional trials study protocol template.

Section 9

This section has been incorporated into "Research Methods" (Section 9) and the numbering has been updated accordingly.

The section has been modified to clarify that data collected for patients included in research projects will be managed according to Appendices 2-7.

Sections 9.2 and 9.4 have been moved to "Quality Control" section (Section 9.8) in order to ensure alignment with non-interventional trials study protocol template. Sections 9.9 and 9.10 have been added to specify the research methods limitations and other aspects, respectively.

Section 10

The title of the section has been changed from "Statistical Methods" to "Data Analysis". This section has been incorporated into "Research Methods" (Section 9) and the numbering has been updated in order to ensure alignment with non-interventional trials study protocol template.

The section has been further modified to specify that in case of data collected from research projects, the analysis might be performed by third parties as described in Appendices 2-7.

Section 11

The title of this section has been changed from "Ethical considerations and administrative procedures" to "Protection of human subjects" in order to ensure alignment with non-interventional trials study protocol template.

The section 11.5 has been moved to a new section entitled "Plans to disseminating and communicating study results"(Section 12) in order to ensure the alignment with the non-interventional trial template.

The section 11.10 has been modified to clarify the members of the Operational Team.

Section 12

The section has been added in order to ensure the alignment with the non-interventional trial template.

Section 13

The reference's list has been updated.

Section 14

Table 14-2 has been updated according to Investigator's Brochure Edition No 13.

Table 14-3, sections 14.9.4 and 14.18.2 have been updated according to the current Afinitor/Votubia® Risk Management Plan V9.0/V8.0.

Sections 14.2, 14.4 14.12, 14.14, 14.17 have been updated with the current cross-reference to the main protocol.

Sections 14.7.1, and 14.7.2 has been modified to amend the age until which pediatric patients are planned to be followed up from 15 for females and 16 for males to 16 for females and 17 for males to comply with EMA request.

Section 14.7.1 and 14.18.1 have been modified to specify that enrollment for TOSCA PASS sub-study will continue until 150 patients are recruited in the sub-study.

Section 14.7.1 and 14.9.2 has been updated according to the current version of SmPC.

Section 14.18.1 has been modified to specify the process for transferring the Adverse Event information to Novartis.

Annex 2

The ENCePP checklist for study protocols has been updated

Sections 16-22

These sections have been added to incorporate the research projects background and rationale, methods, design and duration.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

5.2 Summary of previous amendments

Amendment 2

Amendment Rationale

This amendment includes the following modifications requested by the European Medicines Agency (EMA), (request received on 03 June 2013 as part of the procedure EMEA/H/C/2311/REC014):

- To extend the TOSCA disease registry and the TOSCA PASS observation period for all the pediatric patients residing in the European Union included in the TOSCA PASS until they reach Tanner stage V if evaluated per local routine practice or until age 15 for females or 16 for males, regardless of the end of treatment therapy, in order to collect long term data on sexual maturation and fertility. In particular the TOSCA database will be maintained open up to 15 years only to grant the data collection for the pediatric patients included in the TOSCA PASS until they reach Tanner stage V if evaluated per local routine practice, or until age 15 for females or 16 for males, regardless of the end of treatment therapy. Patients not included in the TOSCA PASS sub-study or with an age greater than 15 for females or 16 for males or at Tanner stage V will be followed-up for up to 5 years from the date of enrolment.
- To clarify that everolimus Therapeutic Drug Monitoring (TDM) data will be collected within routine clinical practice as per Summary of Product Characteristics (SmPC). TDM will be evaluated, using a validated assay, as per local procedures.
- To include in the statistical analysis the evaluation of the relationship between everolimus blood levels and the incidence of events of special interest and concomitant antiepileptic medication

To update the list of events of special interest according to the Risk Management Plan (RMP) version 9/7. For any further RMP update affecting the list of Adverse Events (AEs) of special interest, no protocol amendments will be issued immediately, while a notification letter will be sent to the Investigators. Any Investigator Brochure (IB) update will be released to the Investigators and any safety information update will be communicated.To clarify that data to fulfill the objectives of the TOSCA registry will be collected for all TSC patients included in the TOSCA registry. In addition, long-term safety data of treatment with prescribed Votubia® in the licensed indications will be collected for patients participating to the TOSCA PASS sub-study to fulfill the objectives of the TOSCA PASS sub-study. The analyses for the TOSCA registry objectives like [redacted] Additional changes to the protocol are:

- To replace [redacted] as protocol author
- To add [redacted] as protocol author
- To adapt the PASS protocol to the template provided by EMA and based on Art 38 of Implementing Regulation No 520/2012 with the additional instructions of Module VIII of the Good Pharmacovigilance Practices (GVP)

- To specify that AEs ongoing at the time of the Inform Consent Form (ICF) signature or occurring after the ICF signature will be collected in the TOSCA PASS sub-study
- To correct typographical and grammatical errors as well as protocol inconsistencies

Changes to the protocol

Changes to the specific sections of the protocol are shown in the track changes version of the protocol using strike through red font errors for deletions, red (underline) for insertions.

Authors:

Replacement of [redacted] as protocol author.

Addition of [redacted] as protocol author.

Cover page, Section 11.1, Section 11.3, from Section 14.1 to Section 14.20:

- Adjustment of the sections to the new template provided by EMA and based on Art 38 of Implementing Regulation No 520/2012 with the additional instructions of Module VIII of the Good Pharmacovigilance Practices (GVP)

Synopsis:

- Update of the Votubia® Risk Management Plan version (RMP Version 9/7 May 2013)
- Clarification that everolimus Therapeutic Drug Monitoring (TDM) data will be collected within routine clinical practice as per SmPC
- Extension of the observation period for the pediatric patients included in the TOSCA PASS, until they reach Tanner stage V, or until age 15 for females or 16 for males
- Clarification that the analyses for the TOSCA registry objectives like [redacted]
- Update of the list of AEs of special interest as per RMP Version 9/7, May 2013
- Update of the disease registry and TOSCA PASS milestones
- Specification that follow-up of initial and additional patients after the closure of the TOSCA PASS could be conducted by Novartis or possibly by a third party organization, including a non-profit organization

Section 2:

- Update of the Votubia® Risk Management Plan version (RMP, Version 9/7 May 2013)

Section 3 :

- Update of the list of AEs of special interest as per RMP Version 9/7 May 2013
- Clarification that everolimus Therapeutic Drug Monitoring (TDM) data will be collected within routine clinical practice as per SmPC
- Clarification that the analyses for the TOSCA registry objectives like [redacted]

[redacted]

Section 4:

- Extension of the observation period for the pediatric patients included in the TOSCA PASS, until they reach Tanner stage V, or until age 15 for females or 16 for males

Section 4.1:

- Clarification that the analyses for the TOSCA registry objectives like [redacted]

Section 4.3:

- Extension of the observation period for the pediatric patients included in the TOSCA PASS, until they reach Tanner stage V, or until age 15 for females or 16 for males
- Specification that follow-up of initial and additional patients after the closure of the TOSCA PASS could be conducted by Novartis or possibly by a third party organization, including a non-profit organization

Section 14.6:

- Update of the list of AEs of special interest as per RMP Version 9/7 May 2013
- Clarification that everolimus Therapeutic Drug Monitoring (TDM) data will be collected within routine clinical practice as per SmPC

Section 14.7.1:

- Extension of the observation period for the pediatric patients included in the TOSCA PASS, until they reach Tanner stage V, or until age 15 for females or 16 for males

Section 14.7.2:

- Update of the end of study definition

Section 14.9.3:

- Addition of the evaluation of the [redacted]

Section 14.9.4:

- Update of the list of AEs of special interest as per RMP Version 9/7 May 2013
- Addition of the following outcome: [redacted]

Section 14.9.11:

- Update of the list of AEs of special interest as per RMP Version 9/7 May 2013

Section 14.18:

- Clarification that AEs ongoing at the time of the Inform Consent Form (ICF) signature or occurring after the ICF signature will be collected in the TOSCA PASS sub-study

Section 14.18.2:

- Update of the list of AEs of special interest as per RMP Version 9/7 May 2013
- Clarification that for any further RMP update affecting the list of AEs of special interest, no protocol amendments will be issued immediately, while a notification letter will be sent to the Investigators.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 1

Amendment Rationale

The main objectives of this amendment are:

- To ensure alignment of the original protocol to the new European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practices – Module VI (Management and reporting of adverse reactions to medicinal products).
- To comply with the EMA's request (EMEA/H/C/002311/II/0004) to collect in the TOSCA disease registry data on the long-term safety of the prescribed treatment with Votubia® (everolimus) in the licensed indications, to characterize the important identified risks, potential risks (e.g. male infertility) and missing information listed in the Votubia® Risk Management Plan (RMP). Patients in the European Union participating in the TOSCA disease registry will enter a TOSCA safety sub-study, classified as Post Authorisation Safety Study (PASS), if they are on prescribed treatment with Votubia® in the licensed indications at the time of enrolment in the TOSCA disease registry or as soon as they start prescribed treatment with Votubia® in the licensed indications after enrolment in the TOSCA disease registry. Treatment with Votubia® will be an inclusion criterion only for participants in the TOSCA safety sub-study (PASS). The main purpose of the TOSCA PASS is to [redacted]

Additional changes to the protocol are:

- To add [redacted] as protocol authors.
- To exclude patients currently participating in interventional Novartis sponsored clinical trials with everolimus in TSC in order to avoid any double entry of disease, safety and efficacy data in two different Novartis databases may lead to reconciliation issues further complicated by the unknown treatment assigned in case of double-blind clinical studies. If a patient participating in the TOSCA disease registry starts treatment with everolimus in an interventional Novartis sponsored clinical trial, the patient follow up will be suspended until the end of study visit specified in the interventional Novartis sponsored clinical trial.
- To extend participation in the TOSCA disease registry to other countries worldwide, e.g., Australia, China, South Africa, Russia, Turkey, Korea, Taiwan, New Zealand, Thailand, Malaysia and to adjust accordingly the patients number and the sites number participating in the registry
- To extend the anticipated enrollment period in the TOSCA disease registry from 18 to 24 months to ensure an enrollment period of at least 12 months for all participating countries.
- To specify that the follow-up of initial and additional patients, for more than five years, could be conducted by Novartis or possibly by a third party organization, including a non-profit organization
- To adapt the original TOSCA disease registry protocol to the new Novartis template for non-interventional studies referenced in the Novartis Standard Operative Procedure SOP-7015232, v1 25 Jul 2012.
- To update the TOSCA disease registry Organization structure as agreed during the TOSCA Scientific Advisory Board roundtable with TSC experts and Patient Association Group (PAG) representatives held in Naples, Italy on 06th September, 2012.

- To clarify that all efforts will be done in order to maintain the same subject number in case the patient is re-screened by another site.
- To clarify that the first administrative interim analysis is foreseen when complete data collection for the baseline 'Core' data set for 100 patients are entered into the registry database
- To correct typographical and grammatical errors as well as protocol inconsistencies

Changes to the protocol

Changes to the specific sections of the protocol are shown in the track changes version of the protocol using strike through red font errors for deletions, red (underline) for insertions

Authors:

- Addition of [redacted] as protocol author

Cover page, Synopsis, Section 2, Section 5, Section 5.3, Section 7.2.1, Section 7.3, Section 8.1, Section 9.3, Section 9.4, Section 10, Section 11, Section 11.1, Section 11.2, Section 12:

- Adjustment of the sections to the new Novartis template for non-interventional studies according to a Novartis Standard Operative Procedure(SOP-7015232, v1 25 Jul 2012)

Synopsis:

- Addition of the TOSCA PASS rationale
- Addition of the object to collect information, on sexual maturation/endocrine assessments in patients with TSC
- Addition of the TOSCA PASS objectives
- Addition of the TOSCA PASS population
- Adjustment of the patients number, sites and countries participating in the registry
- Addition of the number of TOSCA PASS patients
- Extension of the enrollment period in the registry from 18 to 24 months
- Addition of the TOSCA PASS design
- Addition of the TOSCA PASS statistical considerations

Section 2:

- Extension of the Registry participation in other countries worldwide
- Addition of the TOSCA PASS rationale.

Section 3:

- Deletion of the following variables in the objective aimed to record TSC interventions and outcomes: [redacted]
- Addition of the object to [redacted]

- Addition of the TOSCA PASS objectives

Section 4:

- Addition of the TOSCA PASS study design
- Extension of the Registry participation in other countries worldwide
- Extension of the enrolment period in the registry from 18 to 24 months
- Specification that follow-up of initial and additional patients for more than five years could be conducted by Novartis or possibly by a third party organization, including a non-profit organization

Section 4.2:

- Renaming of the Steering Committee to Scientific Advisory Board
- Clarification that the first administrative interim analysis is foreseen when complete data collection for the baseline 'Core' data set for 100 patients are entered into the registry database

Section 4.3:

- Extension of the enrolment period in the registry from 18 to 24 months
- Specification that follow-up of initial and additional patients for more than five years could be conducted by Novartis or possibly by a third party organization, including a non-profit organization

Section 5:

- Extension of the Registry participation in other countries worldwide

Section 5.1:

- Specification that concurrent participation of patients in interventional Novartis sponsored clinical trial with everolimus in TSC is not allowed. Patients previously treated with everolimus through the Individual Patient Supply Program (IPSP) or enrolled in an Expanded Access Study Novartis sponsored and switched to commercial drug supply are eligible.

Section 5.2:

- Addition of the exclusion criteria regarding the participations in the TOSCA disease registry of patients currently participating in interventional Novartis sponsored clinical trials with everolimus in TSC

Section 6.3.1 and Section 7.2.1:

- Clarification that all efforts will be done in order to maintain the same subject number in case the patient is re-screened by another site

Section 7.1.2:

- Specification that only class of drug , except for Votubia® will be collected in the TOSCA disease registry and that detailed information on Votubia® will be collected in the TOSCA PASS

Section 7.2:

- Addition of the reference to the TOSCA PASS in Appendix I

Section 8.1:

- Specification that data on long-term safety of the treatment with Votubia® will be collected in the TOSCA PASS

Section 8.2 and Section 8.3:

- Moving of the Sections 8.2 and 8.3 to the TOSCA PASS (Appendix I)

Section 9:

- Clarification that key sensitive personal identifiable information (e.g. exact date of birth) will be collected only in countries where it is allowed by local regulations

Section 10:

- Deletion of collection of data about treatment with mTOR inhibitor
- Adjustment of the patients number, sites and countries participating in the registry
- Clarification that the first administrative interim analysis is foreseen when complete data collection for the baseline 'Core' data set for 100 patients are entered into the registry database

Section 11.5:

- Adjustment of the publication section in agreement TOSCA disease registry publication policy (reference), agreed during the TOSCA roundtable held in Naples, Italy on 06th September, 2012

Section 11.10, Section 11.10.1, Section 11.10.2, Section 11.10.3, Section 11.10.4

- Adjustment of the TOSCA disease registry overall organization in agreement with the charters (reference), agreed during the TOSCA roundtable held in Naples, Italy on 06th September, 2012

References:

- Updating of the references

Appendix I:

- Addition of the TOSCA PASS

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

6 Milestones

Milestones planned dates

Milestone	Planned Date
Start of data collection	10-Aug-2012
End of data collection for the patients included in the disease registry and for patients included in the TOSCA PASS who already reached Tanner stage V or age of 16 for females and 17 for males at the time of end of data collection	10-Aug-2017
Study progress report(s)	Yearly update
Interim report(s) of study results, if applicable	Yearly update
Final report results of patients included in the disease registry	December 2017
End of data collection for the pediatric patients included in the TOSCA PASS	10-Aug-2027
Final report results of patients included in the TOSCA PASS	December 2027

7 Rationale and Background

7.1 Overview of disease pathogenesis, epidemiology and current treatments

Tuberous Sclerosis Complex (TSC) is an autosomal dominant genetic disorder caused by inactivating mutations in the tuberous sclerosis complex tumor suppressor genes, TSC1 or TSC2, affecting tuberin and hamartin respectively. The results of a second somatic mutation in the heterozygous background include benign, highly vascular, hamartomatous growths.

Lesions occur in the brain, kidneys, heart, liver, lungs and skin, and phenotypically can manifest with renal and or pulmonary complications, autism, mental retardation and epilepsy (Gomez et al, 1999; Astrinidis and Henske, 2005; Inoki et al, 2005; Kwiatkowski and Manning, 2005). Measures of childhood prevalence range from 1 in 6,800 to 1 in 17,300 but full ascertainment is difficult to achieve (Yates 2006). Brain lesions are the primary cause of morbidity and mortality in this disorder in childhood. After neurologic manifestations, renal lesions are the most common cause of morbidity and mortality in TSC (Franz 2004).

In 1998, a panel of international experts revised the diagnostic criteria for tuberous sclerosis complex at the Tuberous Sclerosis Complex Consensus Conference in Annapolis, Maryland (Roach ES 1998; Hymann MH et al 2000). The revised criteria (Table 7-1) reflect an improved understanding of the clinical manifestations of tuberous sclerosis complex and its genetic and molecular mechanisms. The diagnostic criteria are based on the premise that there are probably no truly pathognomonic clinical signs for TSC; signs that were once regarded as specific occur as isolated findings in individuals with no other clinical or genetic evidence of TSC. Consequently, the revised criteria require TSC–associated lesions of two or more organ systems or at least two dissimilar lesions of the same organ to confirm the diagnosis. The criteria do not include symptoms such as seizures or mental retardation to avoid "double counting" (i.e., central nervous system lesions cause seizures, and including both in the criteria leads to counting the same symptom twice). Associated neurologic features also include autism or pervasive developmental disorders, mental retardation, and various learning and behavioural disorders.

Table 7-1 Revised Diagnostic Criteria for Tuberous Sclerosis Complex

Major features
1. Facial angiofibromas or forehead plaque 2. Nontraumatic ungual or periungual fibroma 3. Hypomelanotic macules (three or more) 4. Shagreen patch (connective tissue nevus) 5. Multiple retinal nodular hamartomas 6. Cortical tuber* 7. Subependymal nodule 8. Subependymal giant cell astrocytoma 9. Cardiac rhabdomyoma, single or multiple 10. Lymphangiomyomatosis† 11. Renal angiomyolipoma†
Minor features
1. Multiple randomly distributed pits in dental enamel 2. Hamartomatous rectal polyps‡ 3. Bone cysts§ 4. Cerebral white-matter "migration tracts"*§

5. Gingival fibromas 6. Nonrenal hamartoma‡ 7. Retinal achromic patch 8. “Confetti” skin lesions 9. Multiple renal cysts‡
Definite tuberous sclerosis complex: Either two major features or one major feature plus two minor features. Probable tuberous sclerosis complex: One major plus one minor feature. Possible tuberous sclerosis complex: Either one major feature or two or more minor features.
*When cerebral cortical dysplasia and cerebral white-matter migration tracts occur together, they should be counted as one rather than two features of tuberous sclerosis. †When both lymphangiomyomatosis and renal angiomyolipomas are present, other features of tuberous sclerosis should be present before a definite diagnosis is assigned. ‡Histologic confirmation is suggested. §Radiographic confirmation is sufficient.

The second International Tuberous Sclerosis Complex Consensus Conference was held June 13-14, 2012, in Washington, DC with 79 specialists from 14 countries, to revise diagnostic, surveillance, and management recommendations for patients with TSC (Northrup and Krueger 2013; Krueger and Northrup 2013). One of the major goals of the conference was to revisit the clinical diagnostic criteria published subsequent to the first International TSC Consensus Conference in 1998. Key changes compared with 1998 criteria are the new inclusion of genetic testing results and reducing diagnostic classes from three (possible, probable, and definite) to two (possible, definite). Additional minor changes to specific criterion were made for additional clarification and simplification (Table 7-2).

Table 7-2 Updated diagnostic criteria for tuberous sclerosis complex 2012

A. Genetic diagnostic criteria The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of tuberous sclerosis complex (TSC). A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment ([www.lovd.nl/TSC1], [www.lovd/TSC2], and Hoogeveen-Westerveld et al., 2012 and 2013). Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria, and are not sufficient to make a definite diagnosis of TSC. Note that 10% to 25% of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC.
B. Clinical diagnostic criteria Major features 1. Hypomelanotic macules (≥3, at least 5-mm diameter) 2. Angiofibromas (≥3) or fibrous cephalic plaque 3. Ungual fibromas (≥2) 4. Shagreen patch 5. Multiple retinal hamartomas 6. Cortical dysplasias* 7. Subependymal nodules 8. Subependymal giant cell astrocytoma 9. Cardiac rhabdomyoma 10. Lymphangioleiomyomatosis (LAM)§ 11. Angiomyolipomas (≥2) Minor features 1. “Confetti” skin lesions 2. Dental enamel pits (>3) 3. Intraoral fibromas (≥2) 4. Retinal achromic patch 5. Multiple renal cysts 6. Nonrenal hamartomas

Definite diagnosis: Two major features or one major feature with ≥2 minor features **Possible diagnosis**: Either one major feature or ≥2 minor features
* Includes tubers and cerebral white matter radial migration lines. § A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis

7.1.1 Neurologic Manifestations

The predominant neurologic manifestations of TSC are mental retardation, epileptic seizures, and behavioral abnormalities, but affected individuals with little or no neurologic impairment are common (Gomez et al 1999; Curatolo et al 2003). Neurologic lesions probably result from impaired neuronal migration along radial glial fibers and from abnormal proliferation of glial elements. Neuropathologic lesions of TSC include subependymal nodules (SEN), subependymal giant cell astrocytoma (SEGA), cortical hamartomas, areas of focal cortical hypoplasia, and heterotopic gray matter (Weiner et al 1998; Takanashi et al 1995). Although all of the superficial cerebral lesions of TSC are sometimes lumped together as cortical tubers, the actual pathologic picture is more complex. A classic tuber is a dysplastic lesion of a gyrus that has a firm, nodular feel; it often occurs at the apex of a gyrus but does not always enlarge the gyrus. However, areas of focal cortical dysplasia that are not nodular and are less sharply demarcated are common, ranging from grossly visible defects of the cortical mantle to microscopic disruption of the cytoarchitecture. Various types of seizures occur in 80 to 90% of patients. Most patients with mental retardation have epilepsy, but there are exceptions. On the other hand, many people with TSC have epilepsy but have normal intelligence.

The number of subependymal lesions does not correlate with the clinical severity of TSC, but patients with numerous lesions of the cerebral cortex shown by magnetic resonance imaging (MRI) tend to have more cognitive impairment and more difficulty with seizure control. Children with infantile spasms are more likely to exhibit long-term cognitive impairment, but these patients, in turn, have more cortical lesions demonstrated by MRI.

The likelihood of mental retardation in patients with TSC is probably overestimated. The severity of intellectual dysfunction ranges from borderline to profound mental retardation. Autism and various behavioral disturbances, including hyperactivity, aggressiveness, and frank psychosis, are common, either as isolated problems or in combination with epilepsy or intellectual deficit.

The incidence of SEGA in TSC varies from 5 to 15% (Shepherd et al 1991). SEGA lesions are usually associated with TSC. They arise in the subependymal layer of the lateral ventricle and are usually located near the foramen of Monro and enhance homogeneously with contrast on MRI with no evidence of surrounding edema. These are slowly growing lesions that are typically unapparent clinically until they reach sufficient size to produce ventricular obstruction and hydrocephalus. By the time symptoms are noted they are often irreversible even by emergent surgical intervention. They arise deep within the brain in the region of the foramen of Monro, which hampers their surgical resection, as the approach to the lesion entails removal of substantial amounts of viable cerebral tissue. Surgery, even when successful, often results in significant morbidity. For SEGAs that exhibit serial growth, cause hydrocephalus, or produce any clinical symptoms, resection is currently the only recommended treatment for these patients (Torres et al 1998; Sinson et al 1994; Cuccia et al 2003). The lack of reported spontaneous regression or subsequent stabilization in SEGAs supports this recommendation (Franz 2007). In addition, SEGAs do not typically respond to radiation therapy or chemotherapy (Franz 2007). Given the genetic basis of TSC, the risk of

inducing second malignancies through utilization of standard chemotherapeutic agents or radiation therapy has been noted (Matsumura et al 1998).

In the SEGA population, antiepileptic drugs are often used in an attempt to control the frequency of epileptiform events, but this class of drugs does not address the underlying pathology and has no effect on tumor burden.

7.1.2 Renal Manifestations

The kidneys are one of the most frequently involved organs. Two types of renal involvement are recognized. Polycystic kidney disease occurs in 3 to 5% of individuals with TSC and it is distinct from single or multiple renal cysts, which occur much more commonly in TSC. In polycystic kidney disease, innumerable cysts are present, which largely replace the renal parenchyma. Patients develop progressive renal insufficiency and hypertension and, ultimately, require renal transplant. Because persons with polycystic kidney disease have so few functioning renal parenchyma, they are highly susceptible to intercurrent processes, such as kidney stones or infections. An acute urinary tract infection or renal stone can provoke a sudden deterioration in renal function or even kidney failure. Polycystic kidney disease tends to present in infancy and childhood (Franz, 2004).

Renal angiomyolipomas (AML) are the most common renal manifestation of TSC occurring in about 75 to 80% of patients with TSC over the age of 10 years; most of these lesions are histologically benign tumors with varying amounts of vascular tissue, fat, and smooth muscle (Ewalt et al. 1998). The majority of adults have multiple bilateral lesions which are usually asymptomatic but can cause life-threatening hemorrhage or impaired renal function. AML can occur in the liver but these are rarely of clinical significance (Yates, 2006).

Patients with TSC appear to be at increased risk of renal cell carcinoma, estimated at 1to 3% (Nelson and Sanda, 2002).

There are two morbidities associated with renal AML. The first and more dramatic is Wunderlich syndrome (Chesa Ponce et al, 1995), retro-peritoneal hemorrhage originating in the AML. AML, as they enlarge, frequently develop both micro- and macroaneurysms which can rupture (Adler et al, 1984; Bissler et al, 2002). Patients with this sudden, painful, and often life-threatening event are most often first seen in the emergency department (Bissler and Kingswood, 2004). It was estimated that up to 20% of patients with such hemorrhages present in shock (Pode, 1985). With such a presentation, the treatment may be a total nephrectomy. This approach complicates the patient's long-term care. AML associated with TSC are usually bilateral and a nephrectomy would result in a significant loss of functional renal tissue, thus hastening the need for renal replacement therapy (Bissler and Kingswood, 2004). A population study suggests that the cumulative risk of a hemorrhage is 18% for females and 8% for males (Webb et al, 1994). However, among a clinic population of approximately 310 adult and pediatric tuberous sclerosis complex patients in Cincinnati, only nine cases of hemorrhage (~ 3%) were observed (Bissler and Kingswood, 2004). This difference may be, at least in part, due to an aggressive embolization program, population age differences or length of follow-up.

AML appear to grow over time, and there is an association between lesion size and hemorrhage (Steiner et al, 1993; Dickinson et al, 1998).

The second morbidity of renal AML is the insidious encroachment of the angiomyolipoma on normal renal tissue, which may lead to renal failure. The precise incidence of end-stage renal disease (ESRD) in the TSC population has not been well defined, but European surveys suggest that approximately 1% of the TSC patient population with normal intellect is receiving dialytic renal replacement therapy, leading to an estimate that over 30,000 TSC patients are on dialysis worldwide (Schillinger and Montagnac, 1996; Clarke et al, 1999).

The primary reason to intervene in patients with renal AML has been to alleviate symptoms such as pain or hemorrhage. The recent urological literature has embraced a renal sparing approach for AML (Nelson and Sanda, 2002). Key to the long-term outcome of patients with multiple renal AML is the preservation of renal function. Indications for a total nephrectomy are limited and include a nonfunctioning kidney resulting in uncontrolled hypertension, local tissue invasion, tumor in the renal vein, or very strong evidence of malignancy. Partial or nephron-sparing nephrectomies run the risk of significant hemorrhage, and therefore should be undertaken only if unequivocally indicated. Embolization is currently regarded as a suitable alternative to such invasive procedures. The procedure obliterates the blood supply to the angiomyolipoma and thus reduces the risk of hemorrhage. Nevertheless, embolization also has significant side effects. In a review of published series, it was estimated that 85% of patients develop post-embolization syndrome, including significant fever and pain (Bissler and Kingswood, 2004). In addition, although embolization and surgical therapies can successfully treat solitary lesions, the much more vexing clinical problem of coalescent renal angiomyolipomata that replace renal parenchyma has remained largely unaddressed. When bleeding occurs in this circumstance, it can be impossible to identify which lesion is the source.

7.1.3 Pulmonary Manifestations

At least 1% of patients TSC develop symptomatic pulmonary dysfunction, and many others probably have asymptomatic lung lesions on diagnostic studies later in life. The classic pulmonary lesion of TSC is lymphangioleiomyomatosis (LAM); other patients have multifocal micronodular pneumocyte hyperplasia.

LAM is a rare disorder related to abnormal function of the *TSC1* and *TSC2* genes. Mutations in the *TSC2* gene generally are thought to be the cause of sporadic LAM (that is, in patients with no evidence of TSC) (Smolarek et al, 1998; Carsillo et al, 2000). Although LAM has been recognized more as a sporadic, noninheritable pulmonary disorder, it also occurs in about one third of women with TSC (Costello et al, 2000; Moss et al, 2001; Franz et al, 2001). In patients with TSC, LAM predominantly affects premenopausal women and is very rare in men (Hancock et al, 2002). Normal lung is replaced by numerous cysts and histologically there is diffuse proliferation of smooth muscle-like cells in the remaining alveolar septa. Sporadic LAM is a relatively uncommon disease with a prevalence that has been estimated at 2.6 per 1 million women (Urban et al, 1999). However, the disease progression in TSC-associated LAM may be different from the sporadic form as only approximately 1% of women with TSC develop clinical symptoms (Hancock et al, 2002).

Data suggest that LAM cells can metastasize; identical mutations in *TSC2* were found in lung lesions and angiomyolipomata from the same patient with sporadic LAM, and recurrent LAM cells of recipient origin were detected in the donor lung of a transplanted patient (Maruyama, 2001; Karbowniczek et al, 2003; Bittmann et al, 2003). Although the “primary” source of

LAM cells in the lungs is unknown, the potential sources include angiomyolipomata and the lymphatic system (Henske, 2003).

Approximately 60% of patients with sporadic LAM also have an AML (Bernstein and Robbins, 1991). The AML histopathologic features seen in sporadic LAM are identical with those found in TSC (Chan et al, 1993). Both TSC associated and sporadic LAM are characterized by smooth muscle infiltration into the walls of the alveoli and small airways. This can lead to cystic degeneration of lung tissue, impaired gas exchange, respiratory failure, and death. Progressive symptomatic lung disease may occur in patients diagnosed with sporadic LAM and such progression likewise would be predicted to occur in women with TSC-associated LAM (Bissler and Kingswood, 2004). Eventual respiratory failure due to destruction of lung tissue may require lung transplantation, which remains the most viable option for end-stage disease.

7.1.4 Skin Manifestations

The cutaneous lesions of TSC include hypomelanotic macules, the shagreen patch, ungual fibromas, and facial angiofibromas. One or more of these skin lesions occur in over 90% of individuals with TSC, although none is pathognomonic (Roach ES 1998). Hypomelanotic macules (ash leaf spots) are found in over 90% of patients with TSC. They are usually present at birth but are often difficult to see in the newborn without an ultraviolet light. Other pigmentary abnormalities include the "confetti" lesions (an area with stippled hypopigmentation, typically on the extremities) and poliosis of the scalp hair or eyelids. Hypomelanotic macules are not specific for TSC because one or two of these lesions are relatively common in normal individuals (Vanderhooft et al 1996).

Facial angiofibromas occur in about three fourths of patients but often appear several years after the diagnosis has been established by other means. These lesions typically become apparent during the preschool years as a few small red papules on the malar region; they gradually become larger and more numerous, sometimes extending down the nasolabial folds or onto the chin. Angiofibromas contain both vascular and connective tissue elements. Although facial angiofibromas are a strong indication of TSC when found with other manifestations, these lesions also occur in individuals with multiple endocrine neoplasia type I and thus are not pathognomonic for either condition.

The shagreen patch is most commonly found on the back or flank area; it is an irregularly shaped, slightly raised, or textured skin lesion. The lesion is found in 20 to 30% of patients with TSC and occasionally other individuals. It might not be apparent in young children. Ungual fibromas are nodular or fleshy lesions that arise adjacent to or from underneath the nails. The lesion is usually considered specific for TSC, although a single lesion occasionally occurs after trauma. Ungual fibromas are seen in about 20% of unselected patients with tuberous sclerosis complex and are more likely to be found in adolescents or adults than in younger children. Sometimes the fibroma itself is not visible but creates a prominent longitudinal groove in the fingernail, a finding that also has diagnostic significance.

7.1.5 Ophthalmic Manifestations

The frequency of retinal hamartomas in TSC varies with the expertise and technique of the examiner. Under ideal circumstances, up to 87% of patients with TSC have retinal lesions, but especially in uncooperative children, these lesions can be difficult to identify without dilating the pupils and the use of indirect ophthalmoscopy (Kiribuchi et al 1986). Retinal lesions vary

from the classic mulberry lesions adjacent to the optic disk to the plaque-like hamartoma or depigmented areas. Most retinal lesions are clinically insignificant, but occasional patients have visual impairment owing to a large macular lesion, and rare patients have visual loss owing to retinal detachment, vitreous hemorrhage, or hamartoma enlargement. Some patients have a pigmentary defect of the iris.

7.1.6 Cardiac Manifestations

Roughly two thirds of newborns with TSC have one or more cardiac rhabdomyomas, but few of these lesions are clinically important. Cardiac rhabdomyomas are often multiple but shrink over time and are identified much less often in older children and adults (DiMario et al 1996). These lesions are sometimes evident on prenatal ultrasonographic testing, and most of the patients with cardiac dysfunction present soon after birth with heart failure, usually owing to either obstruction of blood flow by an intraluminal tumor or to inadequate normal myocardium to maintain perfusion. Some patients stabilize and improve after medical treatment; others require surgery. A few children later develop cardiac arrhythmias.

7.2 Purpose and Rationale

There is common agreement that there are still gaps in understanding the course of TSC manifestations and their prognostic role, rare symptoms and co-morbidities, interventions, treatments and their outcomes, and quality of life. The registry described in this protocol will address many of these gaps by collecting data from patients across many countries worldwide that would not be sufficient if only collected from patients in an individual country. The data collected might inform patient's treatment standards and flows and research in TSC.

Following the EMA's request (EMEA/H/C/002311/II/0004), data on the long-term safety of the prescribed treatment with Votubia® (everolimus) in the licensed indications will be collected in a TOSCA safety sub-study (Appendix 1) classified as Post-Authorization safety Study (PASS) to characterize the important identified risks, potential risks (e.g. male infertility) and missing information listed in the Votubia® Risk Management Plan (RMP Version 9/7, May 2013). Patients in the European Union participating in the TOSCA disease registry will enter the TOSCA PASS if they are on prescribed treatment with Votubia® in the licensed indications at the time of enrolment in the TOSCA disease registry or as soon as they start prescribed treatment with Votubia® in the licensed indications after enrolment in the TOSCA disease registry. The treatment with Votubia® will be an inclusion criterion only for the participation in the TOSCA safety sub-study (PASS). The main purpose of the TOSCA PASS is to generate long-term safety data during the long-term treatment with Votubia® in patients with TSC in a real life setting in the European Union.

Efficacy information will be collected through the participation to the disease registry sub-studies. For patients enrolled in the TOSCA PASS the collection of information on the disease manifestation for which Votubia® is prescribed will be mandatory including efficacy outcomes.

7.3 Rationale for the registry design

This registry is structured to retrospectively and prospectively collect respective patient and disease information.

A general pre-defined set of patient's background data including demographics, family, prenatal, vital signs and disease features are collected in the 'Core' section of the registry and are mandatory in order to have a minimum of information on each patient for meaningful analyses.

Additional and more detailed data related to specific disease manifestations are collected in sub-sections of the registry.

A yearly update is requested for both the 'Core' section and the sub-sections data, if available.

In order to ensure patients' contribution to this registry, a patient self-report section will collect patient's own additional information and quality of life questionnaires.

8 Research Question and Objectives

Objectives and related main variables under study are described in Table 8-1 below.

Table 8-1 Objectives and related main variables under study

Objectives	Main Variables	Analysis
[redacted]	[redacted]	Refer to Section 9.7
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	

Objectives	Main Variables	Analysis
Additional objective(s)		
[redacted]	[redacted]	Refer to Section 9.7
TOSCA PASS objective(s)		
[redacted]	[redacted]	
[redacted]	[redacted]	

Data to fulfill the objectives of the TOSCA registry will be collected for all TSC patients included in the TOSCA registry. In addition, long-term safety data of treatment with prescribed Votubia® in the licensed indications will be collected for patients participating to the TOSCA PASS sub-study to fulfill the objectives of the TOSCA PASS sub-study. The analyses for the TOSCA registry objectives like [redacted]

Following the approval of Amendment 3, additional data on specific disease manifestations will be collected through the implementation of six research projects developed by the Research Groups (RG). Each Research Project will have specific objectives as reported in Appendix 2 to Appendix 7.

9 Research Methods

9.1 Study design

9.1.1 Description of study design

This registry is designed to collect information on a large international cohort of patients with TSC. The name of the registry is TOSCA - Tuberous Sclerosis registry to increase disease Awareness.

Male or female alive patients of any age with a diagnosis of TSC, with documented visit for the disease within 12 months or newly diagnosed will be enrolled. Registry participating physicians should obtain ICF signature (parental/guardian consent if applicable) to entitle enrollment in the registry.

The registry is structured to collect retrospectively and prospectively patient and disease information.

General mandatory information on patient's background, including demographics, family, prenatal, vital signs and disease features are collected in the 'Core' section of the registry at baseline and updated yearly, if available.

Additional and more detailed data related to specific disease manifestations will be collected in sub-sections (i.e. research projects) of the registry and will be updated yearly or according to the procedures described for each Research Project (Appendix 2 to Appendix 7.). Retrospective and prospective data are therefore collected from both patient characteristics and disease specific information of any subjects enrolled in the registry.

Following an EMA's request (EMEA/H/C/002311/II/0004), data on the long-term safety of the prescribed treatment with Votubia® (everolimus) in the licensed indications will be collected in a TOSCA safety sub-study (Appendix 1) classified as Post-Authorisation Safety Study (PASS) to characterize the important identified risks, potential risks (e.g. male infertility) and missing information listed in the Votubia® Risk Management Plan (RMP). Patients in the European Union participating in the TOSCA disease registry will enter the TOSCA PASS if they are on prescribed treatment with Votubia® in the licensed indications at the time of enrolment in the TOSCA disease registry or as soon as they start treatment with

prescribed Votubia® in the licensed indications after enrolment in the TOSCA disease registry. The treatment with Votubia® will be an inclusion criterion only for participation in the TOSCA safety sub-study (PASS). The purpose of the TOSCA PASS is to generate [redacted] An additional ICF will be signed by these patients to authorize the collection of the long-term safety data.

The data to fulfill the objectives of the TOSCA registry will be collected for all TSC patients included in the TOSCA registry. In addition, long-term safety data of treatment with prescribed Votubia® in the licensed indications will be collected for patients participating to the TOSCA PASS sub-study to fulfill the objectives of the TOSCA PASS sub-study. The analyses for the TOSCA registry objectives like [redacted]

It is estimated that approximately 2000 patients meeting eligibility criteria after informed consent signature will be enrolled in the TOSCA disease registry from approximately 250 sites in more than 30 countries worldwide. This enrollment estimate may vary and will be flexible since no formal sample size is required due to the descriptive nature of this registry and the lack of a specific hypothesis to be tested.

In this registry no clinical instrumental or laboratory assessments/interventions will be performed other than those required for disease management according to local best practice or required to monitor any treatment as per locally approved summary of product characteristics or if patient is taking part in an approved interventional non-Novartis sponsored clinical study in TSC, if applicable. The only exception will be the patient reported outcome questionnaires to assess quality of life (QOL) and burden of illness (BOI) (Research Project 6) and the TAND checklist (Research Project 4). These sub-projects will be launched upon relevant IRB/EC and HA/CA approvals of the protocol amendment 3.

Follow up patient' visits will be scheduled according to the standard practice of the site and to the treating physician's best judgment or as specified in the ongoing non-Novartis sponsored clinical studies. It is assumed that at least a disease assessment every 12 months in the context of regular follow up visits will be performed. Disease evaluation could be performed more frequently, if needed; any valuable information collected at follow up visits will be recorded in the registry.

For each patient enrolled in the registry a minimum of one yearly update (10 ±2 month interval) is scheduled to ensure an ongoing data stream.

Designated registry staff will enter the data into an electronic Case Report Forms (eCRFs) through a web-based internet system using fully validated software that conforms to regulatory requirements for electronic data capture. The initial enrollment period for the disease registry is anticipated to be about 24 months with a follow-up observation period of up to 5 years for the patients not included in the TOSCA PASS sub-study or with an age greater than 16 for females or 17 for males or at Tanner stage V. For the pediatric patients included in the TOSCA PASS, the follow-up period will be extended until they reach Tanner stage V, or until age 16 for females or 17 for males, regardless of the end of treatment therapy, in order to collect long term data on sexual maturation and fertility.

Since the database is ongoing for up to 15 years, retrospective revisions/additions will be possible at any time as additional or corrective data emerges. .

The follow-up of initial and additional patients after the closure of the TOSCA PASS could be conducted by Novartis or possibly by a third party organization, including a non-profit organization.

9.1.2 Timing of interim analyses and design adaptations

The first administrative interim analysis is foreseen when complete data collection for the baseline 'Core' data set for 100 patients are entered into the registry database to check if the mandatory data collection for the 'Core' allows a preliminary meaningful descriptive data analysis. Subsequent interim data cuts are planned approximately every 12 months on the whole database content.

In the future data collected in this registry might be pooled for research-driven analyses with data deriving from other national or international TSC disease registries, upon agreement of Novartis and the Scientific Advisory Board. Information about subjects in the registry will be kept confidential and managed under the applicable laws and regulations.

9.1.3 Definition of end of the study

The initial enrollment period for the disease registry is anticipated to be about 24 months. Upon approval of the protocol amendment 3, the enrollment in the TOSCA registry will be extended over the initial enrollment of 24 months in the countries participating to the TOSCA PASS sub-study to reach 150 patients in the TOSCA PASS. Only patients eligible for the TOSCA PASS will be enrolled in this extended enrollment period.

A follow-up observation period of up to 5 years is foreseen for the patients not included in the TOSCA PASS sub-study or with an age greater than 16 for females or 17 for males or at Tanner stage V. For the pediatric patients residing in the European Union included in the TOSCA PASS the follow-up period will be extended until they reach Tanner stage V, or until age 16 for females or 17 for males, regardless of the end of treatment therapy, in order to collect long term data on safety and sexual maturation and fertility.

The follow-up of initial and additional patients after the closure of the TOSCA PASS could be conducted by Novartis or possibly by a third party organization, including a non-profit organization.

9.1.4 Early registry termination

The registry can be terminated at any time for any reason by Novartis.

The registry participating physician will be responsible for informing IRBs and/or ECs of the early termination of the registry.

9.2 Setting

The TOSCA disease registry is open to TSC patients and it is estimated that approximately 2000 patients meeting the eligibility criteria will be enrolled from approximately 250 sites in

more than 30 countries worldwide. This enrollment estimate may vary since no formal sample size is required for the TOSCA disease registry.

9.2.1 Inclusion criteria

Patients eligible for inclusion in this registry have to meet **all** of the following criteria:

1. Patient with diagnosis of tuberous sclerosis complex
2. Male or female alive patients of any age
3. Patient with a documented visit for TSC within 12 months or newly diagnosed with TSC prior to agreement to participate in the registry by physician-patient ICF signature
4. Patient must sign ICF (parental/guardian consent, if applicable) before any data or information is provided into the registry

Although concurrent participation of patients in clinical trials is allowed, treatment information (except class of drug and duration) on non-Novartis study medication will not be identified in the database. The following information will not be collected: study drug name, dose/dose changes, reason for dose changes, and compliance. All other information regarding the patient's diagnosis, disease status, surgical intervention, other non-proprietary treatment information and response to those treatments will be collected. Concurrent participation of patients in interventional Novartis sponsored clinical trials with everolimus in TSC is not allowed. In case a patient already participating to TOSCA registry is enrolled in any Novartis sponsored interventional clinical trial in TSC or starts receiving everolimus through the Individual Patient Supply Program (IPSP), the patient's data collection in TOSCA will be put on hold until the discontinuation from the interventional clinical trial or IPSP in order to avoid any duplication of data collection. Patients previously treated with everolimus through the Individual Patient Supply Program (IPSP) or enrolled in a Novartis sponsored Expanded Access Study and switched to prescribed Votubia® are eligible.

The registry participating physician must assess whether there is any third-party agreements limiting clinical trial patient's data collection in the registry given that no identification of proprietary treatment information will take place.

9.2.2 Exclusion criteria

Patients eligible for this registry must not meet **any** of the following criteria:

1. According to registry participating physician's opinion the patient is an unlikely candidate to provide follow-up information e.g., for reasons of unavailability.
2. Patients currently participating in interventional Novartis sponsored clinical trials with everolimus in TSC.

9.3 Variables

The main variables are described in Section 8.

9.4 Data source(s)

The data for this study will be retrieved from hospital discharge files, clinical records, electronic medical records, patients' questionnaires, ad hoc clinical databases.

Initiation of the participating sites will be performed by Novartis and/or a designated CROs. Before study initiation, a Novartis representative (or designee) will review the protocol and eCRF with the physicians and their staff.

Sites enrolling patients in this study will record data on eCRF provided by Novartis (or designee) which will capture, check, store and analyze the data.

CROs will follow their own internal Standard Operating Procedures (SOPs) that have been reviewed and approved by Novartis.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

9.4.1 Data Collection schedule

9.4.1.1 Patient numbering

Each patient is identified in the registry by a Subject Number (Subject No.), that is assigned when data for the patient are entered in the data base for the first time and is retained as the primary identifier for the patient throughout his/her entire participation in the registry. Once assigned, the Subject No. must not be reused for any other subject and all efforts will be done in order to maintain the same subject number in case the patient is re-screened by another site.

9.4.1.2 Visit schedule and assessments

In this registry no clinical instrumental or laboratory assessments/interventions will be performed other than those required for disease management according to local best practice or required to monitor any treatment as per locally approved summary of product characteristics or if the patient is taking part of an approved clinical study, if applicable. The only exception will be the patient reported outcome questionnaires to assess quality of life (QOL) and burden of illness BOI (Research Project 6) and the TAND checklist (Research Project 4). These sub-project will be launched upon relevant IRB/EC and HA/CA approvals of the protocol amendment 3.

9.4.1.3 Screening/Enrollment

To minimize the possibility of site imposed bias, registry participating physicians will agree to seek consent for participation of all patients meeting eligibility criteria seen at the site.

9.4.1.3.1 Patient demographics and other baseline characteristics

Upon enrollment into the registry, the baseline **mandatory** 'Core' data to be collected will include:

- Background: Demographics, Enrollment, Clinical Trial Enrollment, TSC Diagnosis, Genotype Family: Mother, Father, Relatives with TSC,
- Prenatal,
- Vital Signs,

- Current disease features, if applicable: neurological, neuropsychiatric, renal, cardiovascular, pulmonary, dermatological and dental, ophthalmological, liver, reproductive, other disease features, rare manifestations, co-morbidities, mTOR inhibitor treatments for which collection of information is foreseen in the CRF in the mandatory core data (only class of drugs entered except for prescribed Votubia® in the licensed indications in the TOSCA PASS).
- Additional and more specialty-related retrospective and current data for each involved organ and/ or body system will be collected in specific sub-sections (e.g., infantile spasms, growing SEGA, genetics, etc.) to measure the main variables of the registry.

Information on treatments (only class of drugs) and procedures other than Votubia® treatment will be entered in the 'Core' section or in the sub-sections of the registry with other disease feature/manifestation data. Detailed information on prescribed Votubia® in the licensed indication will be collected in the TOSCA PASS.

Following the approval of Amendment 3 additional information on specific disease manifestations will be collected at baseline according to the research projects procedures (Appendix 2 to Appendix 7).

9.4.1.4 Follow up Period

The TOSCA disease registry database will be updated yearly regarding patient or disease new information, as applicable. In case a new feature of the disease appears while the patient is followed up, the related information will be added in the 'Core' and in the research projects in the eCRFs, and subsequently updated yearly.

Follow up patient's visits will be scheduled according to the standard medical practice of the site and to the treating physician's best judgment, or as per ongoing non-Novartis sponsored study protocol in TSC, if applicable. It is assumed that at least a disease assessment every 12 months in the context of regular follow up visits will be performed. Disease evaluation could be performed more frequently, if needed; any valuable information collected at follow up visits will be recorded in the registry.

For each patient enrolled in the registry a minimum of one yearly update (10 ±2 month interval) is scheduled to ensure an ongoing data stream.

Any retrospective revisions/additions will be possible at any time as additional or corrective data emerges.

For patients included also in the TOSCA PASS please refer to Appendix I and for patients included also in the research projects please refer to Appendix 2 to Appendix 7.

9.4.1.5 Patient withdrawal

Patients **may** voluntarily withdraw from the registry or be dropped from it at the discretion of the registry participating physician at any time. Patients may be withdrawn from the registry if any of the following occur:

- Death
- Lost to follow up by the site

- Patient withdrew consent

In case a patient is lost to follow up by the site and is re-screened/enrolled in the registry by another site, upon re-signature of the ICF, all efforts will be done in order to maintain the same subject number in case the patient is re-screened by another site.

Each registry participating physician will have access to the data generated from his/her patients. Patients will be identified by a unique ID key. Only physicians will be able to link patients to their ID key. It is the responsibility of each site to keep this list confidential and to update it accordingly for the purpose of facilitating data validation.

All data generated up to the time of voluntary discontinuation (withdrawal of consent) and the reason(s) for discontinuation will be recorded. Patients who choose to withdraw consent will no longer be contacted for follow up information.

9.4.1.6 Assessment types

Effectiveness

This is a disease registry that is not designed to test a formal hypothesis but may generate hypotheses for future studies. Being observational, this registry will investigate outcomes of interventions under real conditions. Further information will be collected in the sub-sections.

Safety

Please refer to Section 11 of the protocol.

Health-related Quality of Life

Upon signature of a specific informed consent, patients will complete questionnaires related to various Patient-Reported Outcomes (PRO) such as validated Quality of Life questionnaires, general and specific for epilepsy, and ancillary questions specific for the disease. These PRO questionnaires will be part of the Research Project 6 that willbe launched upon relevant IRB/EC and HA/CA approvals of the protocol amendment 3 (Appendix 7).

9.5 Study size

It is estimated that approximately 2000 patients meeting eligibility criteria after informed consent signature will be enrolled in the TOSCA disease registry from approximately 250 sites in more than 30 countries worldwide. This enrollment estimate may vary and will be flexible since no formal sample size is required due to the descriptive nature of this registry and the lack of a specific hypothesis to be tested.

9.6 Data management

Designated registry staff will enter the data required by the registry into a secure web-based internet system using eCRF with fully validated software that conforms to regulatory requirements for electronic data capture (EDC). An international Contract Research Organization (CRO) will administer and manage the web-based system and review the data for completeness and accuracy. Queries are expected to be minimal since the web-based

system will have on-line validation checks to minimize data entry errors. Any queries generated will be sent to the site using the web-based system and will provide an automatic audit trail of the corrections made by the designated registry staff.

Data collected for patients included in the research projects will be managed according to the procedures described in Appendix 2 to Appendix 7.

9.6.1 Data confidentiality

Information about subjects in the registry will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this registry
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the registry participating physician, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

The data collection system for this disease registry uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Key sensitive personal identifiable information (e.g. exact date of birth), will be collected only in countries where it is allowed by local regulations. Each registry participating physician will have access to the data generated from his/her patient. Patients will be identified by a unique ID key. Only physicians will be able to link patients to their ID key. It is the responsibility of each site to keep this list confidential and to update it accordingly for the purpose of facilitating data validation.

9.6.2 Data collection

The designated registry site staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Registry site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the registry site staff.

The registry participating physician is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Each participating site will maintain appropriate medical and research records for this registry, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participation in a

Novartis-sponsored disease registry, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the registry progress.

Source data are all information, original records of clinical findings, observations, necessary for the reconstruction and evaluation of the disease registry.

Data collection is the responsibility of the TOSCA disease registry staff at the site under the supervision of the site registry participating physician. The registry eCRF is the primary data collection instrument for the registry. The registry participating physician should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. For electronic CRFs an audit trail will be maintained by the system.

The registry participating physician /institution must keep medical records of enrolled patients in the registry and take appropriate measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for the duration of the disease registry unless Sponsor provides written permission to dispose of them or requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

Data collection for patients included in the research projects will be managed according to the procedures described in Appendix 2 to Appendix 7.

9.7 Data Analysis

All analyses will be performed by Novartis personnel or designated CRO. In case of data collected from research projects, the analysis might be performed by other third parties according to what described in Appendix 2 to Appendix 7.

All patients enrolled in the TOSCA disease registry will be considered in the analysis.

Demographic and clinical parameters will be tabulated for the descriptive statistical analyses of relevant variables. Given the descriptive nature of this registry and the lack of a specific hypothesis to be tested, there is no formal sample size calculation. Data will be summarized with respect to the background (demography, TSC diagnosis, genotype, familiarity, pre-natal diagnosis and mortality), clinical features (neurological, neuropsychiatric, renal, cardiovascular, pulmonary, dermatological, ophthalmological, liver, reproductive, ...), rare manifestations, co-morbidities and to detailed data related to specific disease manifestations collected in theresearch projects.

Each variable will be analyzed overall and in terms of annual prevalence and annual incidence, taking as reference a calendar year, and change from the baseline visit. One-way table and two-way contingency table will be the preferred approach to present results.

Any further stratification to elucidate the relationship among 3 or more items and to identify and characterize specific sub-groups of scientific interest related to

diagnostic/prognostic/interventions factors, entailing the employment of more advanced statistical models will be exclusively data-driven, and will take place after the evaluation of the first administrative interim analysis results. The registry is indeed exploratory in its nature and therefore no strong hypotheses to be tested are currently in place.

In general, missing data will not be imputed. For the date variables of historical data (i.e. any data referring to the period prior to the informed consent date), if the year part is missing then the value will not be imputed. For the partial missing situation (month or day missing), the value will be imputed for the analysis purpose. The month will be imputed with June and the day will be imputed with day of 15th in general.

The sample size is not based on statistical considerations. It is estimated that approximately 2000 patients will be recruited from approximately 250 sites in more than 30 countries worldwide. This recruitment estimate may vary and will be flexible, due to exploratory nature of the disease registry.

The first administrative interim analysis is foreseen when complete data collection for the baseline 'Core' data set for 100 patients are entered into the registry database with the subsequent ones planned approximately every 12 months.

Any other aspect related to data conventions, methods of analyses, algorithm for derived variables, etc. will be well documented in the statistical analysis plan.

9.8 Quality control

9.8.1 Site monitoring

Before TOSCA disease registry initiation, at a site initiation visit or at a registry participating physician's meeting, Novartis personnel (or designated CRO) will review the protocol and eCRFs with the physicians and their staff. Monitoring is expected to be minimal except where required according to local regulations. During the conduct of the registry, the field monitor will visit the site at least once per year to check patient records, the accuracy of key entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice, and the progress of enrollment. Key registry personnel must be available to assist the field monitor during these visits.

All information recorded on eCRFs should be traceable to source documents in the patient's file. The registry participating physician must also keep the original signed informed consent form (a signed copy is given to the patient).

The registry participating physician must give the monitor access to all relevant source documents, with exception of proprietary or confidential information related to non-Novartis investigational study drugs, to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the registry-specific monitoring plan.

9.8.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by registry site staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the registry site via the EDC system. Designated registry site staff is required to respond promptly to queries and to make any necessary changes to the data.

9.9 Limitations of the research methods

The anticipated number of enrolled patients in the TOSCA PASS is an estimation subjected to adjustments.

9.10 Other aspects

Not applicable

10 Protection of human subjects

Information about subjects in the registry will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this registry
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the registry participating physician, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

The data collection system for this disease registry uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Each registry participating physician will have access to the data generated from his/her patient. Patients will be identified by a unique ID key. Only physicians will be able to link patients to their ID key. It is the responsibility of each site to keep this list confidential and to update it accordingly for the purpose of facilitating data validation

10.1 Regulatory and ethical compliance

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in non-interventional studies are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke et al 2008), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' (European Medicines Agency 2010).

10.2 Responsibilities of the registry participating physician and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before disease registry start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before enrollment initiation. Prior to disease registry start, the registry participating physician is required to sign a protocol signature page confirming his/her agreement to participate in the disease registry and follow disease registry requirements in accordance with these documents and all of the instructions found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

If an inspection of the registry site is requested by a regulatory authority, the registry participating physician or other involved health care professional must inform Novartis immediately that this request has been made.

10.3 Informed consent procedures

Eligible patients may only be included in the registry after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the disease registry to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before any data are collected. The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide the registry participating physician in a separate document with a proposed ICF that is considered appropriate for this disease registry and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the registry participating physician must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

10.4 Discontinuation of the registry

Novartis reserves the right to discontinue this registry under the conditions specified in the registry agreement.

10.5 Registry documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this registry, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored disease registry, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the registry progress.

Source data are all information, original records of clinical findings, observations, necessary for the reconstruction and evaluation of the disease registry.

Data collection is the responsibility of the disease registry staff at the site under the supervision of the site registry participating physician. The registry eCRF is the primary data collection instrument for the registry. The registry participating physician should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. For electronic CRFs an audit trail will be maintained by the system.

The registry participating physician /institution must keep medical records of enrolled patients in the registry and take appropriate measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for the duration of the disease registry unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

10.6 Confidentiality of disease registry documents and patient records

The registry participating physician must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

10.7 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

10.8 Financial disclosures

Financial disclosures should be provided by registry staff personnel directly involved in the patients' data entry at the site - prior to registry enrollment start.

10.9 Overall Organization

[redacted]

Figure 10-1 [redacted]

10.9.1 Scientific Advisory Board (SAB)

The SAB consists of members who represent the geographic distribution of the Registry as well as the multidisciplinary nature of the disease.

The SAB is responsible for the scientific principles of the registry, promotion of the use of the registry in the participating sites, publication of data in agreement with the publication policy, approval of the research projects. They will meet at least once a year in a plenary session and by ad hoc Teleconference meetings (TCs).

The SAB is chaired by a chairman and a vice-chairman elected every 2 years from the members of the SAB.

Further details on the role and responsibilities of the SAB are defined in the SAB Charter (RADOO1MIC03 SAB charter v2.0, dated 29 May 2014).

10.9.2 Working Committee (WC)

The WC is a sub-group made up of members of the SAB.

It is delegated the task of working on the details of the registry structure, its content and operational protocol.

The WC is responsible for the definition of the Statistical analysis plan, developing and maintaining database structure of the registry in collaboration with other colleagues, according to their specialty and research interests.

Further details on the role and responsibilities of the WC are defined in the WC Charter (RADOO1MIC03 WC charter v2.0, dated 29 May 2014).

10.9.3 Research Group (RG)

A RG is constituted by a variable number of registry participating physicians.

A RG is responsible for the submission of a Research Project Proposal to the SAB, and for the development and the promotion of its research projects among the Registry participating sites.

The RG coordinates presentations and publications activities related to its research projects according to the Publication Policy.

Further details on the role and responsibilities of the RG are defined in the RG Charter agreed during a TOSCA roundtable held in Naples, Italy on 6th September, 2012(RADOO1MIC03 RG charter final version dated 15th October 2012).

10.9.4 Operational Team

The Operational Team will consist of Novartis headquarter clinical trial team that works in close collaboration with the local trial teams and the external vendors.

The Operational Team is responsible for the set up and overall coordination of the project, site training, registry set up, validation and maintenance, data analyses and support to the preparation of publications.

The Operational Team will have regular TCs and ad hoc face to face meetings.

10.10 Protocol adherence and amendments

Treating physician or other involved health care professionals will apply due diligence to avoid protocol deviations. The protocol should be amended and updated as needed throughout the course of the study. Any change or addition to the protocol requires a written protocol amendment that must be approved by Novartis, the principal investigator and the relevant IRB/IEC/REB before implementation. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB must be kept informed of such administrative changes.

11 Management and reporting of adverse events/adverse reactions

11.1 Adverse events

An adverse event is defined as any untoward medical occurrence that does not necessarily have a causal relationship with a treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease whether or not related to a medicinal product

Following the EMA's request (EMEA/H/C/002311/II/0004), data on th [redacted] Patients in the European Union participating in the TOSCA disease registry will enter the TOSCA PASS if they are on treatment with prescribed Votubia® in the licensed indications at the time of enrolment in the TOSCA disease registry or as soon as they start treatment with prescribed Votubia® in the licensed indications after enrolment in the TOSCA disease registry.

Please refer to Section 14.5.2 in Appendix 1 for Votubia® safety monitoring and reporting.

The TOSCA disease registry does not require treatment with a particular drug for inclusion. Drugs are reported only by class of drugs and not identified. Being TOSCA a disease registry without any Novartis drug of interest no solicited safety data capture is required. However, if during the course of the TOSCA disease registry participation an adverse event suspected to be associated with the use of a Novartis product is identified in a patient, it must be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting and notified to Novartis as a spontaneous report.

11.2 Serious adverse events

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization

12 Plans of disseminating and communicating study results

A first administrative interim analysis, planned when data from 100 patients are entered, will be aimed at evaluating feasibility and efficacy of data collection procedure. The subsequent analyses planned approximately every 12 months will be focused on registry aims. Results will be submitted for publication and/or posted in a publicly accessible database of disease registry results.

Novartis has sole ownership of all data, results, reports, and any other information collected and will maintain full access to the database of the Registry, as such access shall be defined from time to time by Novartis.

Publications will be based on data from all sites, analyzed as stipulated in the protocol. Registry participating physician agree not to present data gathered from one site or a small group of sites before the global publication, unless formally agreed to by all other physicians and Novartis.

Regional and local publications are permitted once the global publication for each interim data summary or aggregate thereof has been published:

Further details about the publication of TOSCA disease registry results are reported in the Registry Publication Policy agreed by the Scientific Advisory Board members during a TOSCA roundtable held in Naples, Italy on 6th September, 2012 (RADOO1MIC03 Publication Policy final version dated 15th October 2012). In the future data collected in this registry might be pooled for research-driven analyses with data deriving from other national or international TSC disease registries, upon agreement of Novartis and the Scientific Advisory Board. Information about subjects in the registry will be kept confidential and managed under the applicable laws and regulations.

13 References (available upon request)

Adler J, Greweldinger J, Litzky G (1984): Macroaneurysm in renal angiomyolipoma: Two cases, with therapeutic embolization in one patient. Urol Radiol; 6: 201-3

Astrinidis A, Henske EP (2005) Tuberous sclerosis complex: linking growth and energy signaling pathways in human disease. Oncogene; 24: 7475-7481.

Bernstein J, Robbins TO (1991). Renal involvement in tuberous sclerosis. Ann New York Acad Sci; 615: 36-49

Bissler JJ, Racadio J, Donnelly LF, et al (2002): Reduction of postembolization syndrome after ablation of renal angiomyolipoma. Am J Kidney Dis; 39: 966-71

Bissler JJ, Kingswood JC. Renal angiomyolipomata (2004) Kidney Int; 66: 924-34.

Carsillo T, Astrinidis A, Henske EP (2000) Mutations in the tuberous sclerosis complex gene TSC2 are a cause of sporadic pulmonary lymphangioleiomyomatosis. Proc Natl Acad Sci USA.; 97: 6085-90.

Bittmann I, Rolf B, Amann G, et al (2003). Recurrence of lymphangioleiomyomatosis after single lung transplantation: new insights into pathogenesis. Hum Pathol; 34: 95-8

Chan JK, Tsang WY, Pau MY, et al (1993) Lymphangiomyomatosis and angiomyolipoma: Closely related entities characterized by hamartomatous proliferation of HMB-45-positive smooth muscle. Histopathology; 22: 445-455.

Chesa Ponce N, Artiles Hernandez JL, Ponce Socorro JM, et al (1995). Wunderlich's syndrome as the first manifestation of a renal angiomyolipoma. Arch Esp Urol; 48: 305-308

Clarke A, Hancock E, Kingswood C, et al (1999). End-stage renal failure in adults with the tuberous sclerosis complex. Nephrol Dial Transplant; 14: 988-91.

Commission Implementing Regulation (EU) No 520/2012 on the performance of Pharmacovigilance Activities provided for in Regulation (EC) 726/2004 and Directive 2001/83/EC.

Costello LC, Hartman TE, Ryu JH (2000). High frequency of pulmonary lymphangioleiomyomatosis in women with tuberous sclerosis complex. Mayo Clin Proc; 75: 591-4

Cuccia V, Zuccaro G, Sosa F, et al (2003) Subependymal giant cell astrocytoma in children with tuberous sclerosis. Childs Nerv Syst Apr; 19(4): 232-43.

Curatolo P, Bombardieri R, Jozwiak S. (2008) Tuberous Sclerosis. Lancet; 372: 657-68

Curatolo P (ed) (2003): Tuberous Sclerosis Complex: From Basic Science to Clinical Phenotypes. London, Mac Keith Press

Crino PB. (2006) The tuberous sclerosis complex. N Engl J Med; 355:1345-56.

Dickinson M, Ruckle H, Beaghler M, et al (1998): Renal angiomyolipoma: Optimal treatment based on size and symptoms. Clin Nephrol; 49: 281-286

DiMario FJ, Diana D, Leopold H, Chameides L (1996) Evolution of cardiac rhabdomyoma in tuberous sclerosis complex. Clin Pediatr; 35:615–619

European Medicines Agency (2010) The ENCePP Code of Conduct. Available from: <http:/encepp.eu/code_of_conduct/documents/ENCePPCodeofConduct_20100912.pdf > (Accessed 19 Oct 2010)

Ewalt DE, Sheffield E, Sparagana SP, et al: (1998) Renal lesion growth in children with tuberous sclerosis complex. J Urol; 160: 141–145

Franz DN (2004) Non-Neurologic Manifestations of Tuberous Sclerosis Complex. Journal of Child Neurology / Volume 19, Number 9, September 2004

Franz DN, Brody A, Meyer C, et al. (2001): Mutational and radiographic analysis of pulmonary disease consistent with lymphangioleiomyomatosis and micronodular pneumocyte hyperplasia in women with tuberous sclerosis. Am J Respir Crit Care Med; 164: 661-8.

Franz DN (2007). Tuberous Sclerosis. http://www.emedicine.com/neuro/topic386.htm.

Gomez MR, Sampson JR, Whittemore VH (eds) (1999): Tuberous Sclerosis Complex. New York, Oxford University Press.

Hancock E, Tomkins S, Sampson J, Osborne J (2002) Lymphangioleiomyomatosis and tuberous sclerosis. Respir Med; 96: 7- 13.

Henske EP (2003) Metastasis of benign tumor cells in tuberous sclerosis complex. Genes Chromosomes Cancer; 38: 376-381.

Hoogeveen-Westerveld M, Ekong R, Povey S, et al. Functional assessment of TSC2 variants identified in individuals with tuberous sclerosis complex. Hum Mutat. 2013;34:167-175

Hymann MH, Whittemore VH (2000) National Institutes of Health consensus conference: Tuberous sclerosis complex. Arch Neurol; 57:662–665

Inoki K, Corradetti MN, Guan K-L (2005) Dysregulation of the TSC-mTOR pathway in human disease. Nature Genetics; 37: 19-24.

ISPE (2008) Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf; 17:200-8.

Karbowniczek M, Astrinidis A, Balsara BR, et al. (2003) Recurrent lymphangioleiomyomatosis after transplantation: genetic analyses reveal a metastatic mechanism. Am J Respir Crit Care Med; 167: 976-82.

Kiribuchi K, Uchida Y, Fukuyama Y (1986) High incidence of fundus hamartomas and clinical significance of a fundus score in tuberous sclerosis. Brain Dev; 8:509–517

Krueger DA, Northrup H, The International Tuberous Sclerosis Complex Consensus Group. Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013;49:255-265

Kwiatkowski DJ, Manning BD (2005). Tuberous Sclerosis: a GAP at the crossroads of multiple signaling pathways. Human Molecular Genetics; 14: R1-R8

Maruyama H, Seyama K, Sobajima J, et al (2001) Multifocal micronodular pneumocyte hyperplasia and lymphangioleiomyomatosis in tuberous sclerosis with a TSC2 gene. Mod Pathol; 14: 609-14.

Matsumura H, Takimoto H, Shimada N, et al. (1998) Glioblastoma following radiotherapy in a patient with tuberous sclerosis. Neurol Med Chir (Tokyo); 38: 287-91.

Moss J, Avila NA, Barnes PM, et al (2001) Prevalence and clinical characteristics of lymphangioleiomyomatosis (LAM) in patients with tuberous sclerosis complex. Am J Respir Crit Care Med; 164: 669-71.

Northrup H, Krueger D. The International Tuberous Sclerosis Complex Consensus Group. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013;49:243-254.Nelson CP, Sanda MG (2002): Contemporary diagnosis and management of renal angiomyolipoma. J Urol; 168: 1315-25.

Orlova. Ann NY Acad Sci 2010; 1184:87-105.

Pode D, Meretik S, Shapiro A, et al (1985). Diagnosis and management of renal angiomyolipoma. Urol; 25: 461-7

Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol. 1998; 13(12):624-628

Schillinger F, Montagnac R (1996). Chronic renal failure and its treatment in tuberous sclerosis. Nephrol Dial Transplant; 11: 481-5.

Shepherd, CW et al (1991) Subependymal giant cell astrocytoma: A clinical, pathological and flow cytometric study. Neurosurgery; 28: 864-868.

Sinson G, Sutton LN, Yachnis AT, et al (1994) Subependymal giant cell astrocytomas in children. Pediatr Neurosurg; 20: 233-9.

Smolarek TA, Wessner LL, McCormack FX, et al. (1998). Evidence that Lymphangiomyomatosis is caused by TSC2 mutations: chromosome 16p13 loss of heterozygosity in angiomyolipomata and lymph nodes from women with lymphangiomyomatosis. Am J Hum Genet; 62: 810-5.

Steiner MS, Goldman SM, Fishman EK, et al (1993). The natural history of renal angiomyolipoma. J Urol; 150: 1782-6

Takanashi J, Sugita K, Fujii K, Niimi H: MR evaluation of tuberous sclerosis: Increased sensitivity with fluid-attenuated inversion recovery and relation to severity of seizures and mental retardation. AJNR Am J Neuroradiol 1995;16:1923–1928.

Torres OA, Roach ES, Delgado MR, et al: Early diagnosis of subependymal giant cell astrocytoma in patients with tuberous sclerosis. J Child Neurol 1998;13:173–177.

Urban T, Lazor R, Lacronique J, et al (1999) Pulmonary lymphangioleiomyomatosis: a study of 69 patients. Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). Medicine (Baltimore); 78: 321-37.

Vandenbroucke JP, von Elm E, Altman DG, et al (2007) Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. Ann Intern Med; 147:W-163-W-194.

Vanderhooft SL, Francis JS, Pagon RA, Sybert VP: Prevalence of hypomelanotic macules in a healthy population. J Pediatr 1996;129:355–361

Webb DW, Kabala J, Osborne JP (1994): A population study of renal disease in patients with tuberous sclerosis. Br J Urol; 74: 151-4

Weiner DM, Ewalt DE, Roach ES, Hensle TW: The tuberous sclerosis complex: A comprehensive review. J Am Coll Surg 1998; 187:548–561.

Yates JRW (2006) Tuberous sclerosis. Europ J Hum Gen; 14:1065-73.

14 Appendix 1 - TOSCA Post-Authorization Safety Study (PASS)

Oncology Region Europe

RAD001/Everolimus/Votubia®

Non-interventional Study Protocol CRAD001MIC03

A post authorization safety study to evaluate the long- term safety of Votubia® in patients with Tuberous Sclerosis Complex participating in the TOSCA Disease Registry

Protocol version identifier	Version 02
Date of last version of protocol	30 July 2014
EU PAS register number	ENCePP number 3247
Active substance	RAD001/everolimus
Medicinal product	Votubia®
Product reference	Votubia®
Procedure number	EMEA/H/C/002311
Marketing authorization holder(s)	Novartis Pharma A.G. Lichtstrasse 35, 4056 Basel, Switzerland
Joint PASS	No
Research questions and objectives	Following the EMA's request (EMEA/H/C/002311/II/0004), data on th [redacted]

[redacted]

PASS objectives:

- [redacted]
- [redacted]

Country (-ies) of study	Countries participating both in the TOSCA disease registry and in the TOSCA PASS sub-study: Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Poland, Slovenia, Spain, Sweden, UK
Country (-ies) of study	Countries participating both in the TOSCA disease registry and in the TOSCA PASS sub-study: Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Poland, Slovenia, Spain, Sweden, UK
Author	[redacted]

[redacted]

Marketing authorization holder(s)

Marketing authorization holder(s)	Novartis A.G. Lichtstrasse 35, 4056 Basel, Switzerland
MAH contact person	[redacted]

List of abbreviations

AE	Adverse Event
CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DS&E	Drug Safety and Epidemiology
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EMA	European Medicines Agency
GCP	Good Clinical Practice
ICF	Informed Consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
PAG	Patient Association Group
PASS	Post-Authorization Safety Study
PHI	Protected health information
PRO	Patient-reported Outcomes
RAP	Report Analysis Plan
REB	Research Ethics Board
RG	Research Group
SAB	Scientific Advisory Board
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
TSC	Tuberous Sclerosis Complex
WC	Working Committee

14.1 Responsible parties

Table 14-1 Main responsible parties

Role	
Main protocol author	[redacted]
Principal investigator (PI)	[redacted]
MAH contact person	[redacted]

14.2 Abstract

Please refer to the Abstract section of the protocol.

14.3 Amendments and updates

Please refer to the Amendment's section of the protocol

14.4 Milestones

Please refer to Section 6 of the protocol

14.5 Rationale and background

14.5.1 mTOR pathway and TSC

The mTOR (mammalian target of rapamycin) protein is a key serine-threonine kinase mainly activated via the PI3 kinase pathway through AKT/PKB and the tuberous sclerosis complex (TSC1/2).

The main known functions of mTOR include the following (Bjornsti and Houghton 2004):

- mTOR functions as a sensor of mitogens, growth factors and energy and nutrient levels, facilitating cell-cycle progression from G1-S phase in appropriate growth conditions
- The PI3K (mTOR) pathway itself is frequently dysregulated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors
- The mTOR pathway is involved in the production of pro-angiogenic factors (i.e., VEGF) and inhibition of endothelial cell growth and proliferation
- Through inactivating eukaryotic initiation factor 4E binding proteins and activating the 40S ribosomal S6 kinases (i.e., p70S6K1), mTOR regulates protein translation, including the HIF-1 proteins. Inhibition of mTOR is expected to lead to decreased expression of HIF-1.

The PI3K/AKT/mTOR pathway is known to be dysregulated in numerous proliferative disorders including cancer. Molecular epidemiological studies have also shown that activation of the PI3K/AKT/mTOR pathway is frequently associated with worsening prognosis through resistance to treatment, disease extension and disease progression. A variety of preclinical

models have confirmed the role of this pathway in tumor development. It has also been demonstrated that constitutional activation of kinases such as AKT can lead to inexorable development of cancers resembling those which in patients are characterized by frequent activation of the same kinases. This is complemented by the demonstration of the antitumor activity of kinase inhibitors acting on the pathway *in vitro* and *in vivo* preclinical models.

Two primary regulators of mTORC1 signalling are the oncogene suppressors tuberin-sclerosis complexes 1 and 2 (TSC1, TSC2). Loss of either TSC1 or TSC2 leads to elevated rheb-GTP levels, a ras family GTPase, which interacts with the mTORC1 complex to cause its activation. mTORC1 activation leads to a downstream kinase signalling cascade, including activation of the S6 kinases. In tuberous sclerosis complex syndrome, inactivating mutations in either the TSC1 or the TSC2 gene lead to hamartoma formation throughout the body. TSC1 mutations account for 20–25% of all mutations identified, and TSC2 mutations account for the remainder.

14.5.2 Everolimus

Everolimus (Afinitor®/Votubia®; RAD001) is a selective mTOR (mammalian target of rapamycin) inhibitor that binds to the intracellular protein FKBP-12, forming a complex that inhibits mTOR complex-1 (mTORC1) activity. Inhibition of the mTORC1 signalling pathway interferes with the translation and synthesis of proteins by reducing the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4EBP-1) that regulate proteins involved in the cell cycle, angiogenesis and glycolysis. Everolimus reduces levels of vascular endothelial growth factor (VEGF), which potentiates tumour angiogenic processes.

Everolimus is a potent inhibitor of the growth and proliferation of tumor cells, endothelial cells, fibroblasts and blood vessel-associated smooth muscle cells. Consistent with the central regulatory role of mTORC1, everolimus has been shown to reduce tumor cell proliferation, glycolysis and angiogenesis in solid tumors in vivo, and thus provides two independent mechanisms for inhibiting tumor growth: direct antitumor cell activity and inhibition of the tumor stromal compartment.

Everolimus has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation and was approved in Europe in 2003 under the trade name Certican®, for the prevention of organ rejection in patients with renal and cardiac transplantation.

In oncology, everolimus has been in clinical development since 2002 for patients with various hematologic and non-hematologic malignancies as a single agent or in combination with antitumor agents.

Afinitor® is approved in more than 90 countries including the United States and throughout the European Union in the oncology settings of advanced renal cell carcinoma following progression on or after vascular endothelial growth factor (VEGF)-targeted therapy, and for locally advanced, metastatic or unresectable progressive neuroendocrine tumors of pancreatic origin.

Afinitor® has recently been approved for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ breast cancer) in combination with exemestane after failure of treatment with letrozole or

anastrozole (US) or without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor (Europe).

Everolimus has received an accelerated approval for the treatment of pediatric and adult patients with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected in US and a conditional approval as Votubia® for the treatment of patients aged 3 years and older with SEGA associated with TSC who require therapeutic intervention but are not amenable to surgery in Europe.

This approval was based on a Phase II, single center, open-label study of everolimus therapy

in SEGA in patients with TSC [Study CRAD001C2485]. A clinically meaningful and statistically significant reduction in primary SEGA volume was shown from baseline to Month 6 on independent central review (median reduction 0.80 cm3, $p<0.001$). Seventy five percent (75.0%) of the patients experienced reductions of $\geq$ 30% and 32.1% experienced reductions of $\geq$ 50%. Range of time on study is now 4.7 to 47.1 months.

This data is supported by the core phase results from the international multicenter Phase III placebo controlled study in patients with SEGA associated with TSC [M2301]. The core phase results showed a 34.6% SEGA response rate among the everolimus treated patients versus a 0% response rate among the placebo treated patients ($p< 0.0001$). In addition, no patients receiving everolimus therapy progressed vs. 6 patients (15.4%) on placebo ($p=0.0002$ based on estimated progression-free rates at 6 months). Skin lesions in everolimus-treated patients responded better (41.7%) to treatment relative to those on placebo (10.5%;

$p=0.0004$). Of note, both time to SEGA progression and skin lesion response rate in study [RAD001M2301] could not be interpreted from a formal statistical perspective as the first test (change in number of seizures) in the fixed-sequence testing strategy failed to yield statistical significance; however both outcomes were considered to be large and clinically relevant.

Everolimus has received approval in US also for the treatment of adults with renal angiomyolipoma associated with TSC, who do not require immediate surgery. The approval was based on core phase results of an international multicentre Phase III placebo controlled study in patients with TSC who have AML [RAD001M2302]. The results demonstrated a 41.8% angiomyolipoma response rate among the everolimus treated patients versus a 0% response rate among the placebo treated patients ($p<0.0001$). Median time to angiomyolipoma progression was 11.4 months in the placebo arm and was not reached in the everolimus arm. Angiomyolipoma progressions were observed in 3 patients (3.8%) in the everolimus arm and 8 patients (20.5%) in the placebo arm ($p<0.0001$ based on estimated progression-free rates at 6 months). Estimated progression-free rates at 6 months were 98.4% for the everolimus arm and 83.4% for the placebo arm (hazard ratio [HR] 0.08; 95% CI: 0.02, 0.37; $p<0.0001$). Skin lesions responses were observed only on the everolimus arm (response rate 26.0%; $p=0.0002$).

Everolimus has received approval in Europe for the treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery.

Overall, safety data available from completed, controlled and uncontrolled studies indicate that everolimus is generally well tolerated at weekly or daily dose schedules. The safety profile is characterized by manageable AEs that are generally reversible and non-cumulative.

The two randomized, double-blind, placebo-controlled pivotal phase III studies [CRAD001M2301] and [CRAD001M2302] and the phase II study [CRAD001C2485] have further contribute to the safety profile of Votubia.

The most frequent grade 3-4 adverse reactions (incidence ≥1%) were infections, stomatitis, neutropenia and amenorrhoea.

Table 14-2 shows the incidence of adverse reactions based on pooled data of patients receiving everolimus in the three TSC studies (including both the double-blind and open-label extension phase, where applicable).

Table 14-2 Adverse reactions reported in TSC studies (Novartis source)

Infections and infestations	
Very common	Upper respiratory tract infection, nasopharyngitis, sinusitis, pneumonia
Common	Otitis media, urinary tract infection, pharyngitis, cellulitis, pharyngitis streptococcal, gastroenteritis viral, gingivitis
Uncommon	Herpes zoster, bronchitis viral
Blood and lymphatic system disorders	
Common	Neutropenia, anemia leukopenia, lymphopenia, thrombocytopenia
Immune system disorders	
Uncommon	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Hypercholesterolemia
Common	Hyperlipidemia, decreased appetite, hypophosphatemia, hypertriglyceridemia
Psychiatric disorders	
Common	Insomnia
Uncommon	Aggression
Nervous system disorders	
Common	Headache, dysgeusia
Vascular disorders	
Common	Hypertension, lymphedema
Respiratory, thoracic and mediastinal disorders	
Common	Cough, epistaxis
Uncommon	Pneumonitis
Gastrointestinal disorders	
Very common	Stomatitis[a]
Common	Diarrhea, nausea, vomiting, abdominal pain, oral pain, flatulence, constipation, gastritis
Skin and subcutaneous tissue disorders	
Very Common	Acne
Common	Rash[b], dermatitis acneiform, dry skin
Uncommon	Angioedema
Renal and urinary disorders	
Common	Proteinuria

Reproductive system and breast disorders	
Very Common	Amenorrhea[c], menstruation irregular[c]
Common	Vaginal hemorrhage, menorrhagia, ovarian cyst, menstruation delayed[c]
General disorders and administration site conditions	
Common	Fatigue, pyrexia, irritability
Investigations	
Common	Blood lactate dehydrogenase increased, blood luteinizing hormone increased
Uncommon	Blood follicle stimulating hormone increased

[a] Includes very common: stomatitis, mouth ulceration, aphthous stomatitis; uncommon: gingival pain, glossitis, lip ulceration.
[b] Includes common: rash, rash erythematous; uncommon: erythema, rash macular, rash maculo-papular, rash generalized.
[c] frequency is based upon number of women age 10 to 55 years of age in the safety pool

In clinical studies, everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcome. Reactivation of infection is an expected reaction during periods of immunosuppression.

In clinical studies and post-marketing spontaneous reports, everolimus has been associated with renal failure events (including fatal outcome), proteinuria and increased serum creatinine. Monitoring of renal function is recommended. In clinical studies, everolimus has been associated with haemorrhage events. On rare occasions, fatal outcomes were observed in the oncology setting. No serious cases of renal haemorrhage were reported in the TSC setting.

Additional adverse reactions of relevance observed in oncology clinical studies and post-marketing spontaneous reports, were cardiac failure, pulmonary embolism, deep vein thrombosis, impaired wound healing and hyperglycaemia.

14.5.3 Purpose and Rationale

The purpose of this safety sub-study is to comply with the EMA's request (EMEA/H/C/002311/II/0004), [redacted] Patients in the European Union participating in the TOSCA disease registry will enter this safety sub-study if they are on prescribed treatment with Votubia® in the licensed indications at the time of enrolment in the TOSCA disease registry or as soon as they start prescribed treatment with Votubia® in the licensed indications after enrolment in the TOSCA disease registry. The main purpose of this safety sub-study is to [redacted]

14.6 Research question and objectives

In addition to the TOSCA Registry objectives and related main variables, the objectives and related main variables specific for the PASS sub-study are described in Table 14-3 below.

Table 14-3 Objectives and related main variables under study

Objectives	Main Variables	Analysis
[redacted]	[redacted]	
Other Objectives		
[redacted]	[redacted]	

14.7 Research methods

14.7.1 Study design

This is a non-interventional, multi-center post-authorization safety study conducted in multiple European Union countries to prospectively [redacted] The observation period for the TOSCA PASS is up to 5 years. For the pediatric patients residing in the European Union, the follow-up period will be extended until they reach Tanner stage V, if evaluated per local routine practice, or until age 16 for females or 17 for males, regardless of the end of treatment therapy, in order to collect long term data on sexual maturation and fertility.

It is anticipated that 150 patients meeting eligibility criteria after informed consent signature will be enrolled in the safety sub-study from approximately 100 sites in more than 15 countries in the European Union. Upon approval of the protocol amendment 3, the enrollment in the TOSCA registry will be extended over the initial enrollment of 24 months in the countries participating to the TOSCA PASS sub-study to reach 150 patients in the TOSCA PASS. Only patients eligible for the TOSCA PASS will be enrolled in this extended enrollment period.

In this safety sub-study no clinical instrumental or laboratory assessments/interventions will be performed other than those required for disease management according to local best practice or required to monitor any treatment as per locally approved summary of product characteristics.

Everolimus blood trough level should be evaluated as per local procedures with a validated assay and according to SmPC it is required for patients treated for SEGA approximately 2 weeks after the initial dose, after any change in dose, after initiation of or change in co-

administration of CYP3A4 inducers or inhibitors or after any change in hepatic status (Child-Pugh) and for patients <3 years of age trough concentrations should be monitored at least 1 week after commencing treatment or after any change in dose or pharmaceutical form. Everolimus blood trough level assessments is an option to be considered for patients treated for renal angiomyolipoma associated with TSC after initiation of or change in co-administration of CYP3A4 inducers or inhibitors or after any change in hepatic status (Child-Pugh).

Designated registry staff will enter the data into electronic Case Report Forms (eCRFs) through a web-based internet system using a fully validated software that conforms to regulatory requirements for electronic data capture.

The data collected for the TOSCA PASS will be entered in the TOSCA database.

14.7.2 Study Completion

The sub-study will be considered completed when all the pediatric patients included in the TOSCA PASS will reach Tanner stage V, or age 16 for females or 17 for males.

14.7.2.1 Premature study discontinuation

The patients should be followed until the study completion except if any of the following conditions for early termination are met:

- Death
- Lost to follow-up by the site
- Voluntary discontinuation (withdrawal of patients consent to collect or use their data) from the TOSCA disease registry

All data generated up to the time of voluntary discontinuation (withdrawal of consent) and the reason(s) for discontinuation will be recorded. Patients who choose to withdraw consent will no longer be contacted for follow up information.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the physician should show “due diligence” by contacting the patients and asking them to return for a final safety assessment. Every effort should be made to obtain reason for discontinuation. The physician should document in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

14.8 Setting

14.8.1 Inclusion criteria

Patients eligible for inclusion in this sub-study have to meet all of the following criteria:

1. Patients participating in the TOSCA disease registry
2. Patients on treatment with prescribed Votubia® in the licensed indications in the European Union
3. Patient must sign the TOSCA PASS ICF (parental/guardian consent, if applicable) before any data or information is provided into the safety sub-study

14.8.2 Exclusion criteria

No exclusion criteria other than the ones required for participation in the TOSCA disease registry.

14.9 Variables

14.9.1 Patient demographics/characteristics

Demographic information and vital signs, medical history and current medical conditions are collected in the TOSCA disease registry. Concomitant medications will be collected for the TOSCA PASS if available. Demographic and other baseline characteristics including medical history, for the TOSCA PASS patients population will be available through the TOSCA disease registry database and will be summarized descriptively. Categorical data will be summarized by frequency and percentages. Quantitative data will be summarized by the number of patients (n), mean, standard deviation, median, minimum, maximum.

14.9.2 Medication of interest

The medication of interest is Votubia® (everolimus), a selective mTOR inhibitor. Votubia® received conditional approval in September 2011 in the European Union for the treatment of patients with SEGA associated with TSC who require therapeutic intervention but are not amenable to surgery. The evidence is based on analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated.

Furthermore in Europe everolimus received approval in October 2012, for the treatment of adult patients with renal angiomyolipoma associated with TSC who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery. The evidence is based on analysis of change in sum of angiomyolipoma volume.Information on treatment with Votubia®, including dose, dose changes/interruption will be collected in the TOSCA PASS.

14.9.3 Drug exposure

Data about Votubia® treatment including daily dose, interruptions, dose changes and duration of exposure will be summarized by descriptive statistics and corresponding listing will be presented. Treatment with Votubia® will be at the discretion of the investigator in accordance with the prescribing information.

Concomitant medications will be captured and summarized.

In addition the [redacted] will be explored.

14.9.4 Outcome(s) of interest

The Outcomes of interest for the TOSCA PASS are:

- [redacted]
- [redacted]

- [redacted]
- [redacted]

14.9.5 Safety related measures

This sub-study is non-interventional in nature and does not impose a therapy protocol, diagnostic/therapeutic interventions or a visit schedule. Available data from routine clinical management of the patients will be collected at patients' visits to their site. To maintain adequate data collection, the sites will be encouraged to provide any updated patient data at 3-monthly intervals.

14.9.6 Laboratory evaluation

Any laboratory abnormality occurred during the observation period, will be recorded in the adverse events eCRF.

14.9.7 Analysis of the main objective

14.9.8 Variable

The primary objective of the TOSCA PASS is to [redacted]

The primary variable of the TOSCA PASS is th [redacted]

The incidence of AEs and SAEs will be summarized by system organ class and preferred term using the MedDRA dictionary. Similar summaries will also be produced for treatment-related AEs and SAEs. These listings will cover both events that occur during the on-treatment and post-treatment period. The overall safety observation period will be divided into two mutually exclusive segments:

1. on-treatment period: from day of enrolling into the study to 28 days after last dose of Votubia®.-
2. post-treatment period: starting at day 28+1 after last dose of Votubia®.

14.9.9 Statistical hypothesis, model, and method of analysis

No statistical hypothesis is being tested in this study.

The analysis of the primary variable is described in Section 14.9.8.

14.9.10 Analysis of other objectives

14.9.11 Variables

Other variables are the following:

- [redacted]
- [redacted]

Additional subgroup analyses may be defined in the report analysis plan (RAP).

14.10 Data Source(s)

Sites enrolling patients in this sub-study will record data on eCRFs provided by Novartis (or designee) which will capture, check, store and analyze the data.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system.

Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA terminology).

Safety data will be transferred to Novartis at a frequency as defined in the protocol.

Data collection schedule

This is a non-interventional study and does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients will be treated according to the local prescribing information, and routine medical practice in terms of visit frequency and types of assessments performed and only these data will be collected as part of the sub-study. The treating physician is asked to complete if possible at every patient visit the appropriate eCRF.

For patients who discontinue prematurely, the reason for discontinuation should be determined.

However, the recommended data collection schedule that most likely mirrors the patterns of routine clinical care of most patients being treated with Votubia® is at 3-monthly intervals.

14.11 Study size

The sample size for this study is not based on statistical considerations. It is anticipated that up to approximately 100 sites in about 15 countries in the European Union will participate in

the study, contributing at least 150 patients. The estimated sample size of at least150 patients was chosen based on the expected Votubia® approval and availability in the participating countries. The actual sample size may differ as availability of Votubia® changes.

14.12 Data management

Data collection and management for the TOSCA PASS will be according to Section 9.6 of the main protocol.

Data of the TOSCA PASS will be entered in the TOSCA database.

The field monitor will visit the site according to the Monitoring Plan to check patients record and accuracy of key entries in the eCRF for data requested in the TOSCA PASS.

14.13 Data analysis

All analyses will be performed by Novartis personnel or designated CRO.

Safety set: consists of all patients who had at least one post-baseline safety assessment and were exposed to at least one dose of Votubia® after the enrollment. Note the statement that a patient had no adverse events (on the Adverse Event eCRF) constitutes a safety assessment.

14.14 Quality control

Data quality assurance

The Novartis Data Management or designated CRO will assure database quality by reviewing the data entered into the CRFs by investigational staff for completeness and accuracy, and in accordance with the data validation plan.

Data recording and document retention

In all scenarios, the physician must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. All information entered in the CRF must be traceable to these source documents in the patient's file. The physician must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).The physician must give Novartis (or designee) access to all relevant source documents to confirm their consistency with the CRF entries. No information in source documents about the identity of the patients will be disclosed.

Site monitoring

Site monitoring for the TOSCA PASS will be according to Section 9.8 of the main protocol.

Formal site monitoring will be performed as described in the Monitoring Plan for this study.

The Novartis data management / designated CRO will assure compliance monitoring.

14.15 Limitations of the research methods

The anticipated number of enrolled patients in the TOSCA PASS is an estimation subjected to adjustments.

14.16 Other aspects

Not applicable

14.17 Protection of human subjects

Regulatory and ethical compliance

Please refer to Section 10 of the protocol

Informed consent procedures

Patients may only be included in this sub-study after providing written informed consent (see Section 10 of the main protocol).

This sub-study must be approved by the local IRB/EC and HA/CA.

After IRB/EC approval of the sub-study and authorization from HA/CA (i.e. legal representative of the hospital) to start, the patient can be included.

14.18 Management and reporting of adverse events/adverse reactions

For patients included in the TOSCA PASS sub study and on treatment with Votubia® all adverse events (AEs) ongoing at the time of the Inform Consent Form (ICF) signature or occurring after the ICF signature– including serious adverse events (SAEs) – have to be collected and recorded in the TOSCA database, irrespective of causal association to Votubia®. All safety data AEs and SAEs occurring in association with exposure to Votubia® or other Novartis drug, if applicable, also have to be recorded in the Novartis safety database. Adverse reactions identified for non-Novartis products should be reported to the local health Authority in accordance with national regulatory requirements for individual case safety reporting or the Marketing Authorization Holder; these will not be recorded in the Novartis safety database.

14.18.1 Adverse event reporting

Any untoward medical occurrence in a patient administered the Votubia® that does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of Votubia® , whether or not related to the medicinal product.

Medical conditions/diseases present before starting the treatment with Votubia® are only considered adverse events if they worsen after starting Votubia®.

The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events must be recorded on the AEs case report/case record form (eCRF) with the following information:

1. the severity grade (grade 1-4)
2. its relationship to Votubia® (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)

4. whether it constitutes a serious adverse event (SAE)

In addition, all reports of the following special scenarios are also considered an adverse event irrespective if a clinical event has occurred:

- Drug-drug or drug-food interaction,
- Drug exposure during pregnancy (via the mother or father with or without outcome) see Section 14.18,
- Drug use during lactation or breast-feeding,
- Lack of efficacy,
- Overdose,
- Drug abuse and misuse,
- Drug maladministration or accidental exposure,
- Dispensing errors / Medication errors,
- Off-label use,
- Withdrawal or rebound symptoms

Any treatment of any adverse event should be recorded on the Adverse Event CRF. Some examples of treatment to be recorded are: no action taken (i.e., further observation only); Votubia® dosage adjusted/temporarily interrupted; Votubia® permanently discontinued due to this adverse event; treatment medication adjusted; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the Votubia®, the interventions required to treat it, and the outcome.

Information about common adverse effects already known about the Votubia® can be found in the Summary of Product Characteristics (SmPC). This information will be included in the patient informed consent for sub-study participation and should be discussed with the patient during the sub-study participation as needed.

Information on all AEs is included in the individual patient eCRFs which must be updated and committed in the study database on a periodic basis but not later than once a month.

Cumulative listing containing all AEs entered in the database is generated once per month by the CRO responsible of data management and transferred to Novartis Global DS&E and made available into the Global Novartis Safety Data Base.

14.18.2 Serious adverse event reporting

An SAE is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

  - routine treatment or monitoring of TSC, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of Votubia®
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above e.g. may require treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- transmission of infectious agent via medicinal product

For Votubia® the following events are of special interest for targeted follow-up and should be notified to Novartis DS&E in the same manner as a SAE:

- non-infectious pneumonitis
- severe infections
- hypersensitivity (anaphylactic reactions)
- stomatitis
- wound healing complications
- increased creatinine/proteinuria/renal failure
- hyperglycaemia/new onset of diabetes mellitus
- dyslipidemia
- hypophosphatemia,
- cardiac failure
- cytopenias
- hemorrhages
- thrombotic and embolic events
- female fertility (including secondary amenorrhea)
- pre-existing infections (reactivation, aggravation, or exacerbation)
- safety in patients with hepatic impairment
- postnatal developmental toxicity
- pregnant or breast-feeding women
- intestinal obstruction/ileus
- male infertility
- pancreatitis
- cholelithiasis
- muscle wasting/muscle loss

For any further RMP update affecting the list of AEs of special interest, no protocol amendments will be issued immediately, while a notification letter will be sent to the Investigators. Any safety information update will be communicated to the sites involved in the

TOSCA PASS sub-study. To ensure patient safety, every SAE, regardless of causality assessment, occurring after the patient has provided informed consent and until 28 days after the patient has stopped Votubia® treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 28 day period should only be reported to Novartis if the treating physician or other involved health care professional suspects a causal relationship to the drug of interest.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the treating physician or other involved health care professional receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The treating physician or other involved health care professional must assess the relationship to the drug of interest, complete the SAE Report Form and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety & Epidemiology (DS&E) Department.

The telephone and telefax number of the contact persons in the local department of DS&E, specific to the site, are listed in the treating physician or other involved health care health care professional folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the SmPC a local DS&E Department associate may urgently require further information from the treating physician or other involved health care professional for Health Authority reporting.

14.18.3 Pregnancies

To ensure patient safety, any occurrence of a pregnancy in a patient on Votubia® must be reported to Novartis within 24 hours of learning of its occurrence.The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Pregnancy Form and reported by the treating physician or other involved health care professional to the local Novartis DS&E Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to Votubia® of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form. In case of any congenital abnormality,

birth defect or maternal and newborn complications, the possible relationship to the Novartis drug of interest should be reported.

Pregnancy outcomes must be collected for the female partners of any males who took Votubia® in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

14.19 Plans of disseminating and communicating study results

Interim analyses are planned yearly until TOSCA PASS end.

The final manuscript of the TOSCA PASS will be submitted to EMA and the competent authorities of the Member States in which the product is authorized within two weeks after first acceptance for publication.

14.20 References (available upon request)

Bjornsti and Houghton (2004): The TOR pathway: a target for cancer therapy. Nat Rev Cancer. May;4(5):335-48

15 Annex 1 – List of stand-alone documents

Table 15-1 List of stand-alone documents

Number	Document reference number	Date	Title
1	Annex 3	27 August 2013	Principal investigators and trial sites list for PASS substudy

16 Annex 2 – ENCePP checklist for study protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is “Yes”, the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer ‘N/A’ (Not Applicable) can be checked and the “Comments” field included for each section should be used to explain why. The “Comments” field can also be used to elaborate on a “No” answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document

and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

A post authorization safety study to evaluate the long- term safety of Votubia® in patients with Tuberous Sclerosis Complex participating in the TOSCA Disease Registry

Study reference number:

CRAD001MIC03 - ENCePP number 3247

Section 1: Milestones

	Yes	No	N/A	Protocol Section(s)
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection	☒	☐	☐	Milestones
1.1.2 End of data collection	☒	☐	☐	Milestones
1.1.3 Study progress report(s)	☒	☐	☐	Milestones
1.1.4 Interim progress report(s)	☒	☐	☐	Milestones
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	Milestones

Comments: As EU PAS register was not fully operational, the study was registered in the E-Register of Studies on the 18th of December 2012.

Section 2: Research question

	Yes	No	N/A	Protocol Section(s)
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	14.5.3
2.1.2 The objective(s) of the study?	☒	☐	☐	14.6
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2; 14.8
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments: Given the descriptive nature of this registry, no statistical hypothesis is being tested in this study as per protocol Sections 9.7 and 14.9.9.

Section 3: Study design

	Yes	No	N/A	Protocol Section(s)
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	14.7.1
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	8.1; 14.6
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☒	☐	

Comments: None.

Section 4: Source and study populations

	Yes	No	N/A	Protocol Section(s)
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	14.7.2
4.2.2 Age and sex?	☒	☐	☐	9.2
4.2.3 Country of origin?	☒	☐	☐	Appendix 1
4.2.4 Disease/indication?	☒	☐	☐	14.7.1
4.2.5 Co-morbidity?	☐	☒	☐	
4.2.6 Seasonality?	☐	☒	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	14.8

Comments: None.

Section 5: Exposure definition and measurement

	Yes	No	N/A	Protocol Section(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	☒	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments: In this registry no clinical instrumental or laboratory assessments/interventions will be performed other than those required for disease management according to local best practice or required to monitor any treatment as per locally approved summary of product characteristics.
As a consequence, in the registry everolimus blood trough level data evaluated as per local procedures within routine clinical practice will be collected (see protocol sections 14.7.1 and 14.9.3).
The relationship between everolimus blood level and incidence of events of special interest and concomitant antiepileptic medications will be explored (see protocol section 14.9.4).

Section 6: Endpoint definition and measurement

	Yes	No	N/A	Protocol Section(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	14.9.4; 14.9.2
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments: None.

Section 7: Confounders and effect modifiers

	Yes	No	N/A	Protocol Section(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☒	☐	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	

Comments: None.

Section 8: Data sources

	Yes	No	N/A	Protocol Section(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	14.7.1
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	14.14
8.1.3 Covariates?	☒	☐	☐	9.5
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☒	☐	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☒	☐	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	14.10
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	14.10
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments: None.

Section 9: Study size and power

	Yes	No	N/A	Protocol Section(s)
9.1 Is sample size and/or statistical power calculated?	☐	☒	☐	

Comments: The sample size for this study is not based on statistical considerations. The estimated sample size of at least 150 patients from approximately 100 sites in about 15 countries in the European Union was chosen based on the expected Votubia® approval and availability in the participating countries. The actual sample size may differ as availability of Votubia® changes.

Section 10: Analysis plan

	Yes	No	N/A	Protocol Section(s)
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☐	☒	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	14.9
10.4 Are stratified analyses included?	☒	☐	☐	14.9
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments: None.

Section 11: Data management and quality control

	Yes	No	N/A	Protocol Section(s)
11.1 Is information provided on the management of missing data?	☐	☒	☐	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	14.14
11.3 Are methods of quality assurance described?	☒	☐	☐	14.14
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments: None.

Section 12: Limitations

	Yes	No	N/A	Protocol Section(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	9.5.1
12.1.2 Information biases?	☐	☒	☐	
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	14.7; 14.11
12.3 Does the protocol address other limitations?	☐	☒	☐	

Comments: None.

Section 13: Ethical issues

	Yes	No	N/A	Protocol Section(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	Amendment 2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	9.6.1;14.17

Comments: None.

Section 14: Amendments and deviations

	Yes	No	N/A	Protocol Section(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	Amendment 2 and 3

Comments: None.

Section 15: Plans for communication of study results

	Yes	No	N/A	Protocol Section(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	14.19
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12; 14.19

Comments: None.

17 Appendix 2 – Research Project 1. Characterizing SEGA in TSC with respect to their pattern of growth, their impact on CSF-circulation, their relation to neurologic and cognitive impairments and potential treatment options

17.1 Research Project Rationale

SEGAs are affecting up to 15% of patients with TSC. They can cause early, rapidly progressive, recurrent and life threatening neurologic symptoms and damages, especially by disturbing CSF circulation. There is scarce knowledge about the natural course of SEGA. Factors predictive of SEGA growth or regrowth after surgery or medical treatment are still unknown. SEGA can be removed surgically or their volume can be reduced with mTOR-inhibitors. The risks and benefits as well as the long-term outcomes of both treatments, separate or in combination, are unclear and need further investigation. An observational study using the TOSCA registry can optimize SEGA management by providing more details about the natural course of SEGA and their response to treatment.

17.2 Research Objectives

The objectives of the Research Project are:

- [redacted]
- [redacted]
- [redacted]

17.3 Research Methods

Patients meeting eligibility criteria for TOSCA and with a SEGA assessed with MRI will be enrolled in the Research Project upon signature of a project specific informed consent.

The evaluation of CNS manifestations in TSC and their treatment options is one of the goals of TOSCA. The extension of the limited range of CNS – related topics of the core set by a detailed panel concerning SEGA will help to assess treatment related and prognostic relevant parameters like tumour size, localisation and growth characteristics in a standardized way.

Retrospective data as well as prospective data will be collected.

17.4 Research Project Design

This is a non-interventional, multi-center Research Project conducted in multiple countries to retrospectively and prospectively collect data on the characterization of SEGA in TSC patients participating in the TOSCA disease registry.

In this research project no clinical instrumental or laboratory assessments/interventions will be performed other than those required for disease management according to local best practice or required to monitor any treatment as per locally approved summary of product characteristics.

Upon enrollment into the Research Project, the baseline and retrospective data will be collected. The TOSCA disease registry database will be updated yearly regarding new information on SEGA characterization, as applicable.

Follow up patient's visits will be scheduled according to the standard medical practice of the site and to the treating physician's best judgment, or as per ongoing non-Novartis sponsored study protocol in TSC, if applicable. It is assumed that at least a disease assessment every 12 months in the context of regular follow up visits will be performed. Disease evaluation could be performed more frequently, if needed; any valuable information collected at follow up visits will be recorded in the registry.

Any retrospective revisions/additions will be possible at any time as additional or corrective data emerges.

Designated registry staff will enter the data into the TOSCA electronic Case Report Forms (eCRFs) through a web-based internet system using fully validated software that conforms to regulatory requirements for electronic data capture.

This Research Project will be run in all countries involved in TOSCA and interested in participating to this Research Project.

17.5 Research Project Completion

Data on the characterization of SEGA will be recorded until the end of the collection of data within TOSCA registry (i.e. 10 August 2017).

17.6 Premature discontinuation

The patients should be followed until the study completion except if any of the following conditions for early termination are met:

- Death
- Lost to follow-up by the site
- Voluntary discontinuation (withdrawal of patients consent to collect or use their data) from the TOSCA disease registry or from the Research Project.

All data generated up to the time of voluntary discontinuation (withdrawal of consent) and the reason(s) for discontinuation will be recorded. Patients who choose to withdraw consent will no longer be contacted for follow up information.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the physician should show "due diligence" by contacting the patients and asking them to return for a final safety assessment. Every effort should be made to obtain reason for discontinuation. The physician should document in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

18 Appendix 3 – Research Project 2. Defining the risk factors in renal disease in TSC and the effect of treatment on prognosis

18.1 Research Project Rationale

TSC is characterized by the formation of benign tumors (hamartomas) in multiple organ systems at various points throughout life. The typical neurological lesions and symptoms in TSC include cerebral cortical tubers, subependymal nodules, giant cell astrocytomas, seizures, infantile spasms, autism, mental retardation and behavioral impairment. Other lesions in TSC are lymphangioleiomyomatosis of the lungs, rhabdomyomas of the heart, facial angiofibromas and peri-ungual fibromas of the skin, renal angiomyolipomas (AMLs), cysts and renal cell carcinoma (RCC). After neurologic manifestations the renal manifestations are the most common cause of morbidity and mortality in TSC. Indeed, 48 to 80 % of TSC patients have significant renal involvement including angiomyolipomas (AMLs), renal cysts, malignant tumors and renal insufficiency, representing a major contribution to patient morbidity and mortality. AMLs, composed of adipocytes, abnormal vasculature and smooth muscle cells, are generally seen in the cortex of the kidney. They are observed with a frequency of 68-80%, presenting in childhood and progressing in size during adulthood.

18.1.1 Renal Angiomyolipomas

Renal AMLs are one of the most frequent manifestations of TSC affecting up to 90% of patients. Renal issues have been reported to be the most frequent diagnosis-related cause of death in TSC affected patients. Although there are some data on the lesion size as a risk factor for bleeding (which is the most frequent complication of these lesions), these data originate from small cohorts and do not differentiate the risk regarding localisation and growth rate of tumours. Especially in the light of growing treatment options (including mTOR-inhibitors) a risk stratification regarding the risk of bleeding would be extremely helpful. An observational study will never create an evidence level compared to interventional trials; however, the comparison of the different treatment options regarding their association with reduction in lesion size, relapse rate and bleeding frequency might give valuable hints to optimize the AML treatment in these patients.

18.1.2 CKD (Prematurely impaired GFR)

Although end stage renal disease is quite rare among TSC patients affecting about 1%, earlier stages of CKD (chronic kidney disease) including proteinuria seem to occur much more frequently in those with TSC as reported in several small cohorts studies. However, very little is known about the epidemiology and contributing risk factors for CKD in TSC. Increased knowledge in this topic is vital, as CKD has been found to be an important and independent risk factor for cardiovascular events. Furthermore, very little is known about the underlying pathogenic mechanism for developing CKD in TSC. From the hypothesis that the loss of functional renal tissue results in secondary focal segmental glomerulosclerosis it follows that proteinuria should occur frequently.

18.1.3 LAM

Experimental data from animal models and case reports point towards a potential influence of estrogen on the development of renal tumors in TSC. Development or aggravation of LAM in correlation with the use of exogenous oestrogen has been reported anecdotally and a study on patients with sLAM found a correlation of oral contraceptive use with early appearance of LAM symptoms. Although strength of data is not very high, the ERS's LAM guidelines recommend the avoidance of oestrogen containing contraceptives in LAM patients. Data on TSC patients are very limited. We recently performed a retrospective analysis and found no association between oestrogen use and occurrence or size of renal AML but a significant correlation with LAM. However, data are based on the self-reporting of only 39 patients (Sauter, M et al personal communication). As contraception is a challenge in TSC patients, it would be very welcome to get uniformly structured data derived from a larger number of patients.

18.1.4 Cystic Disease

Renal cysts (occurring in 20-30% of TSC patients) are mostly single or multiple small lesions, rarely being symptomatic. TSC can co-exist with polycystic kidney disease (PKD). The TSC2 gene is adjacent to the PKD1 gene on chromosome 16 and long deletions can involve both genes simultaneously. These cysts are numerous, large and frequently symptomatic, resulting in renal insufficiency and hypertension.

The prevalence of renal (Non-PKD) cystic lesions, i.e. those not associated with PKD, in TSC patients is well known. However, the growth pattern of these lesions and the influence on renal function and blood pressure in children is not described in literature. Moreover, almost no information is available about the differences in the renal phenotype between patients with TSC1 or TSC2 mutations. Finally, there are currently no standardized guidelines for renal long-term follow-up in this population. However, this aspect in the care for these patients is also very important in view of the future role of mTOR-inhibitors on the renal phenotype.

PKD is defined in the TSC context as having the contiguous gene syndrome. i.e. a mutation involving TSC2 and PKD1.

There will be some TSC patients with multiple bilateral cysts on renal imaging in whom the gene mutations are unknown. These patients may or may not have hypertension or a reduced GFR. In the data fields these patients will not be classified as PKD because one of the aims of the study is to ascertain whether multiple bilateral “simple” cysts – without a PKD1 mutation – can cause hypertension or renal failure.

This will be handled in the data fields by not using the diagnostic label PKD unless the patient has a known PKD1 mutation.

18.1.5 Sexual maturation & fertility disorders

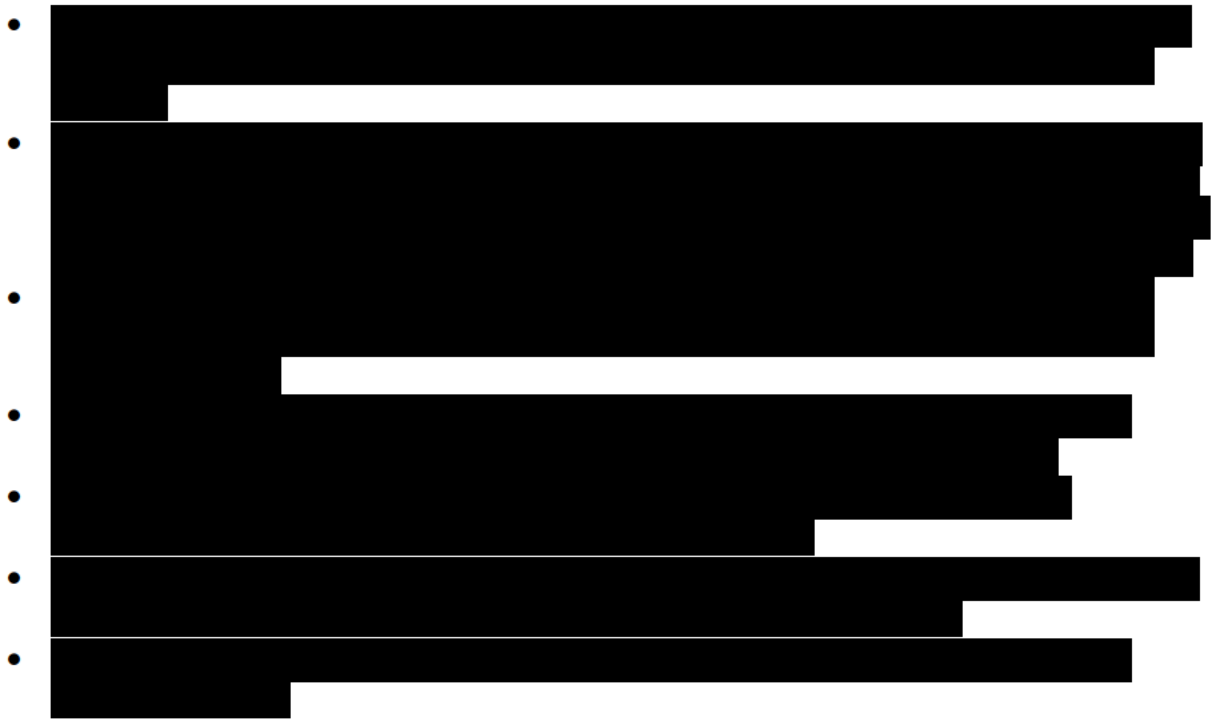
The background prevalence of these problems in the TSC population is of particular interest to physicians who may treat their TSC patients with mTOR inhibitors, because these problems might also be a side effect of mTOR inhibitors.

Hence collaborators in the renal research petal will be encouraged to fill in the relevant fields in the core data as fully as possible. Including in those data fields whether an answer is "Not known" or whether "Not tested" would be helpful. An additional field asking for the results of AMH (Anti Mullerian duct Hormone assay) may be practicable for the prospective study.

18.2 Research Objectives

The renal project has two broad themes: delineating the natural history of the most common complications of TSC renal disease and the effects of treatment.

The objectives of the Research Project are:



18.3 Research Methods

Patients meeting eligibility criteria for TOSCA will be enrolled in the Research Project upon signature of a project specific informed consent. Retrospective data as well as prospective data will be collected.

This Research Project will be run in all countries involved in TOSCA and interested in participating to this Research Project.

18.3.1 Renal angiomyolipoma

Further evaluation of the renal manifestations and their treatment options was identified as a key goal of TOSCA. As the data set on renal features in the core data is very limited, additional data will be collected within the Research Project especially to assess renal angiomyolipoma size, localization and growth in a standardized way.

18.3.2 CKD (Prematurely impaired GFR)

As with AML evaluation of CKD and its treatment options was identified as a key goal of TOSCA. Again the data set on renal features in the core data is very limited, the data panel needs to be extended especially to assess kidney function in a standardized way.

As with AML many questions may be answered with retrospective data (allowing calculations after 1-2 years); prospective data would be very useful in informing treatment protocols.

18.3.3 LAM

Using the TOSCA database only limited additional data fields are necessary to deal with the questions. Only women of age 18 or older will be included in the analysis that comprises correlations of oestrogen intake with presentation of LAM/LAM symptoms or features of renal AML (presence, size, complications) respectively.

Some of the analyses can be performed with retrospective data; prospective data, however, on LAM and kidney issues will be much more useful.

18.4 Research Project Design

This is a non-interventional, multi-center project conducted in multiple countries to retrospectively and prospectively collect data on the the risk factors in renal disease and the effect of treatment on prognosis in TSC patients participating in the TOSCA disease registry.

Patients meeting eligibility criteria for TOSCA will be enrolled in the Research Project upon signature of a project specific informed consent.

In this Research Project no clinical instrumental or laboratory assessments/interventions will be performed other than those required for disease management according to local best practice or required to monitor any treatment as per locally approved summary of product characteristics.

Follow up patient's visits will be scheduled according to the standard medical practice of the site and to the treating physician's best judgment, or as per ongoing non-Novartis sponsored study protocol in TSC, if applicable. It is assumed that at least a disease assessment every 12 months in the context of regular follow up visits will be performed. Disease evaluation could be performed more frequently, if needed; any valuable information collected at follow up visits will be recorded in the registry.

Any retrospective revisions/additions will be possible at any time as additional or corrective data emerges.

Designated registry staff will enter the data into the TOSCA electronic Case Report Forms (eCRFs) through a web-based internet system using fully validated software that conforms to regulatory requirements for electronic data capture.

18.5 Research Project Completion

Data on the risk factors in renal disease will be recorded until the end of the collection of data within TOSCA registry (i.e. 10 August 2017).

18.6 Premature discontinuation

The patients should be followed until the study completion except if any of the following conditions for early termination are met:

- Death
- Lost to follow-up by the site
- Voluntary discontinuation (withdrawal of patients consent to collect or use their data) from the TOSCA disease registry or from the Research Project.

All data generated up to the time of voluntary discontinuation (withdrawal of consent) and the reason(s) for discontinuation will be recorded. Patients who choose to withdraw consent will no longer be contacted for follow up information.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the physician should show “due diligence” by contacting the patients and asking them to return for a final safety assessment. Every effort should be made to obtain reason for discontinuation. The physician should document in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

19 Appendix 4 – Research Project 3. Genotype/Phenotype correlation in TSC

19.1 Research Project Rationale

The genotype in TSC plays a key role in the severity of the disease. Mutations in TSC2 gene are usually associated with a more severe phenotype. On the opposite, some mutations seem to have a milder effect. Nevertheless, conclusions are limited due to the size of the cohorts that were studied. The four largest studies included 224, 276, 325 and 137 patients respectively (Dabora, 2001; Sancak, 2005; Au, 2007 and Van Eeghen, 2012).

The main objective of this project is to [redacted]

In addition, even if TSC tumors (SEGA, AML, LAM, AF) are effectively treated with mTOR inhibitors in most of the patients, the degree of tumor reduction may vary from patient to patient. The role of the genotype in this variability has not been studied yet, thus this project will explore the role of the genotype in the response to mTOR inhibitors in TSC patients.

Cases with intra-familial variability of the disease severity will be collected in order to develop future studies on modifier genes.

19.2 Research Objectives

The primary objective of this project is to [redacted].

Secondary objectives:

- [redacted]
- [redacted]

19.3 Research Methods

Patients meeting eligibility criteria for TOSCA will be enrolled in the Research Project upon signature of a project specific informed consent. The informed consent will explain the aim of the project and how the genetic information will be transferred throughout the project and will include a specific section where the patient can confirm his or her willingness to be informed on the results of the genetic re-evaluation.

The data taken from the report of the genetic test will be recorded in the eCRF of TOSCA study by the site staff. In case the report is not available at the site, it should be obtained from the laboratory where the test was performed. No additional sampling will be performed.

The information on genetic test will be retrieved and re-evaluated by a central laboratory in order to ensure that data collected for all patients are homogenous.

The data collected in the eCRF will be transferred and re-evaluated at the Research Department of Genetics, Evolution and Environment, Darwin Building, University College London, Gower Street, UK (Central Laboratory).

The results of genetic data re-evaluation will be transferred from the Central Laboratory to each clinical site for data entry. In case the patient confirmed his/her willingness in the ICF, he/she will be informed on the genetic re-evaluation results by the investigator or a person delegated by the investigator.

A tracker documenting any discrepancies will be completed by the Central Laboratory and queries will be issued through the database in order to provide the relevant explanation.

This Research Project will be run in European countries involved in TOSCA and interested in participating to this Research Project.

19.4 Research Project Design

This is a non-interventional, multi-center project conducted in multiple European Union countries to prospectively and retrospectively collect data on the genotype/phenotype correlations in TSC patients participating in the TOSCA disease registry.

It is anticipated that patients meeting eligibility criteria for TOSCA after informed consent signature will be enrolled in the Research Project.

In this Research Project no clinical instrumental or laboratory assessments/interventions will be performed other than those required for disease management according to local best practice or required to monitor any treatment as per locally approved summary of product characteristics.

Upon enrollment into the Research Project, data on the gene testing report will be re-evaluated by the Central Laboratory.

Any retrospective revisions/additions will be possible at any time as additional or corrective data emerges.

Designated registry staff will enter the data into the TOSCA electronic Case Report Forms (eCRFs) through a web-based internet system using fully validated software that conforms to regulatory requirements for electronic data capture.

19.5 Research Project Completion

Data on genotype/phenotype correlation in TSC will be recorded once (i.e. no follow up requested) within the end of the collection of data in the TOSCA registry (i.e. 10 August 2017).

19.6 Premature discontinuation

The patients should be followed until the study completion except if any of the following conditions for early termination are met:

- Death
- Lost to follow-up by the site
- Voluntary discontinuation (withdrawal of patients consent to collect or use their data) from the TOSCA disease registry or from the Research Project.

All data generated up to the time of voluntary discontinuation (withdrawal of consent) and the reason(s) for discontinuation will be recorded. Patients who choose to withdraw consent will no longer be contacted for follow up information.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the physician should show "due diligence" by contacting the patients and asking them to return for a final safety assessment. Every effort should be made to obtain reason for discontinuation. The physician should document in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

19.7 References

Au KS et al. Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis complex in the United States.Genet Med. 2007 Feb;9(2):88-100

Dabora SL et al. Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. Am J Hum Genet. 2001 Jan;68(1):64-80.

Sancak O et al., Mutational analysis of the TSC1 and TSC2 genes in a diagnostic setting: genotype--phenotype correlations and comparison of diagnostic DNA techniques in Tuberous Sclerosis Complex. Eur J Hum Genet. 2005 Jun;13(6):731-41.

Van Eeghen AM et al., Genotype and cognitive phenotype of patients with tuberous sclerosis complex. van Eeghen AM, Black ME, Pulsifer MB, Kwiatkowski DJ, Thiele EA. Eur J Hum Genet. 2012 May;20(5):510-5.

20 Appendix 5 – Research Project 4. Exploring the multidimensionality of TSC-Associated Neuropsychiatric Disorders (TAND)

20.1 Research Project Rationale

Neuropsychiatric disorders seen in TSC are some of the top concerns for families and have an enormous impact on quality of life for all who live with the condition. Almost 90% of individuals with TSC will have one or more of these concerns during their lifetime. However, a survey in the UK showed that only 18% of families in contact with the Tuberous Sclerosis Association ever received further evaluations and/or treatment for their neuropsychiatric disorders. These data suggest a □treatment gap□ in excess of 70%.

At the 2012 International Consensus Conference, the Neuropsychiatry Panel commented that such treatment gaps were similar in the HIV community, where there used to be an overemphasis on physical treatment of HIV-positive patients without consideration of the major neuropsychiatric features of HIV. The HIV community introduced the concept of HIV-associated neurocognitive disorders (HAND) as a strategy to raise awareness of such concerns. Inspired by the HIV example, the TSC Neuropsychiatry Panel therefore coined the term TAND (TSC-Associated Neuropsychiatric Disorders) and recommended that all individuals with TSC should be screened for TAND on an annual basis (Krueger and Northrup 2013). In order to facilitate the process a TAND Checklist was developed and pilot validation has recently been completed.

Many professionals and families feel overwhelmed by the complexity of TAND. This may in part be due to the multi-dimensionality of TAND, and in part due to lack of access to clear, useful and evidence-based resources for TAND. In this project the complexity of the TAND checklist will be addressed. We hypothesize that, even though each individual will typically have their own unique TAND profile, there will be key natural TAND Clusters – combinations of behaviours across multi-dimensional levels - that will simplify further evaluations and treatment. This application seeks support to incorporate the TAND Checklist into the TOSCA study. The TAND Checklist will be administered to all participants in the TOSCA registry who will sign the specific informed consent form. Principal component analysis (PCA) will be used for data reduction and factor analysis (FA) to identify natural TAND clusters across age and ability. The identification of natural TAND clusters may be a very helpful first step towards prioritization of clinical concerns and support the generation of treatment guidelines for TAND. TAND cluster analysis may also generate novel hypotheses regarding neuropsychiatric phenomena in TSC to be explored in future studies.

20.2 Research Objectives

The main objective of the study is to [redacted]

The main hypothesis is that [redacted].

20.3 Research Methods

Patients meeting eligibility criteria for TOSCA will be enrolled in the Research Project upon signature of a project specific informed consent.

The administration of the TAND checklist is part of the clinical practice and is described in the TSC surveillance and management recommendation.

The project foresees the annual collection of data of the TAND checklist in consenting patients enrolled in TOSCA. In case the TAND checklist is not administered per local clinical practice to a patient, an appropriate clinician at the clinical site will administer it to the patient.

The data of TAND checklist entered in the registry and demographic data of each patient will be transferred to the Research Fellow based at the University of Cape Town. The research fellow will not have access to identifying information of participants.

Site clinicians will be able to use the TAND Checklist as they see fit for clinical purposes.

TAND Checklist data transferred to the Research Fellow based at the University of Cape Town will be entered into statistical package for the social sciences (SPSS) for analysis as dichotomous and continuous variables as appropriate. Age and developmental level will be added into the model to allow exploration of age and developmental level as possible correlates to specific clusters.

PCA, SPSS and categorical PCA (CatPCA) where appropriate, will then be used. Varimix rotation will be used to minimize variables with high loadings onto principal components. Only variables with loadings >|0.4| will be used. Scree plots will be used for visual examination of data. Ward agglomerative clustering will be used on a Spearman-distance resemblance matrix of ranked PCA scores to generate hierarchical clusters. To determine concordance of PCA dimensions within clusters, Kendall□s (W) test will be used. Potential bivariate associations between PC will be examined using Spearman rank order tests. PCA-FA will therefore identify the optimal number of factors that explain the highest variance. To examine potential differences in factors between clusters (e.g. age as correlate to differential clusters), non-parametric correlations will be used. Given the complexity of PCA-FA, the results will be analyzed with support from a senior statistician.

This Research Project will be run in all countries involved in TOSCA and interested in participating to this Research Project.

20.4 Research Project Design

This is a non-interventional, multi-center project conducted in multiple countries.

In this Research Project no clinical instrumental or laboratory assessments/interventions will be performed other than those required for disease management according to local best practice or required to monitor any treatment as per locally approved summary of product characteristics.

Upon signature of the specific informed consent, the TAND checklist will be administered to a patient if not already done per clinical practice.

Follow up patient's visits will be scheduled according to the standard medical practice of the site and to the treating physician's best judgment, or as per ongoing non-Novartis sponsored study protocol in TSC, if applicable..

Any retrospective revisions/additions will be possible at any time as additional or corrective data emerges.

Designated registry staff will enter the data into electronic Case Report Forms (eCRFs) through a web-based internet system using fully validated software that conforms to regulatory requirements for electronic data capture.

20.5 Research Project Completion

Data of the TAND checklist will be recorded until the end of the collection of data in the TOSCA registry (i.e. August 2017).

20.6 Premature discontinuation

The patients should be followed until the study completion except if any of the following conditions for early termination are met:

- Death
- Lost to follow-up by the site
- Voluntary discontinuation (withdrawal of patients consent to collect or use their data) from the TOSCA disease registry or from the Research Project.

All data generated up to the time of voluntary discontinuation (withdrawal of consent) and the reason(s) for discontinuation will be recorded. Patients who choose to withdraw consent will no longer be contacted for follow up information.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the physician should show "due diligence" by contacting the patients and asking them to return for a final safety assessment. Every effort should be made to obtain reason for discontinuation. The physician should document in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

20.7 References

Krueger DA, Northrup H, The International Tuberous Sclerosis Complex Consensus Group. Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013;49:255-265

21 Appendix 6 – Research Project 5. How TOSCA can help improve the knowledge of epilepsy in TSC

21.1 Research Project Rationale

Epilepsy is the most common presenting symptom in TSC. The majority of children with TSC has onset of seizures during the first year of life, and in most patients in the first few months. Focal seizures precede, coexist with or evolve into infantile spasms (IS). Individuals with TSC2 mutations, as a group, have more tubers, an earlier age at seizure onset, a larger percentage of IS, and more intractable seizures than those with a TSC1 mutation. Early onset of seizures and intractable seizures appears to be associated with an increased risk of neurodevelopmental and cognitive problems. Long-term prognosis of epilepsy in TSC after IS is characterized by intractable seizures in the vast majority of patients, and an increased risk of neurodevelopmental and cognitive problems, including severe mental retardation and autism.

Several options are available for the management of epilepsy in patients with TSC, including anti-epileptic drugs (AEDs), surgery, and (less commonly) ketogenic diet and vagus nerve stimulation. There is a lack of randomized trials for the management of TSC-associated epilepsy. Despite the current pharmacological and non-pharmacological treatment options, one-third of the patients remain resistant to therapy. Among the new treatment options under investigation, mTOR inhibitors provide a potential therapy based on the pathophysiology of TSC. However, limited data is available for epilepsy-related endpoints (e.g. seizure frequency).

Epilepsy negatively impacts not only the health, the quality of life in patient and the family but generates major health costs.

Thus, the limited understanding of the disease and the potential for expanding treatment options provides an appropriate occasion for collecting data on epilepsy in TSC patients in TOSCA registry.

This project will explore in a [redacted].

21.2 Research Objectives

The objectives of the Research Project are:

- [redacted]
- [redacted]
- [redacted]

21.3 Research Methods

Patients meeting eligibility criteria for TOSCA and followed for epilepsy in a clinical site specialized for epilepsy (e.g., specialized site staff for data entry in the registry, EEG reports available,…) will be enrolled in the Research Project upon signature of a project specific informed consent.

[redacted] is one of the goals of TOSCA. Additional data on clinical evaluation, type of seizures, treatment, MRI and neuropsychological testing will be collected retrospectively and prospectively.

This Research Project will be run in all countries involved in TOSCA and interested in participating to this Research Project.

21.4 Research Project Design

This is a non-interventional, multi-center project conducted in multiple countries to prospectively and retrospectively collect data on the epilepsy in TSC patients.

In this Research Project no clinical instrumental or laboratory assessments/interventions will be performed other than those required for disease management according to local best practice or required to monitor any treatment as per locally approved summary of product characteristics.

Upon enrollment into the Research Project, data on clinical evaluation of epilepsy, type of seizures, treatment, EEG, MRI and neuropsychological testing will be collected. Any retrospective revisions/additions will be possible at any time as additional or corrective data emerges.

Designated registry staff will enter the data into the TOSCA electronic Case Report Forms (eCRFs) through a web-based internet system using fully validated software that conforms to regulatory requirements for electronic data capture.

The information collected with the validated questionnaires of the quality of life in epilepsy questionnaires within the Research Project 6 (Appendix 7) might be analyzed with epilepsy data of the core and of this Research Project.

21.5 Research Project Completion

Data on epilepsy in TSC will be recorded until the end of the collection of data within TOSCA registry (i.e., 10 August 2017).

21.6 Premature discontinuation

The patients should be followed until the study completion except if any of the following conditions for early termination are met:

- Death
- Lost to follow-up by the site
- Voluntary discontinuation (withdrawal of patients consent to collect or use their data) from the TOSCA disease registry or from the Research Project.

All data generated up to the time of voluntary discontinuation (withdrawal of consent) and the reason(s) for discontinuation will be recorded. Patients who choose to withdraw consent will no longer be contacted for follow up information.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the physician should show “due diligence” by contacting the patients and asking them to return for a final safety

assessment. Every effort should be made to obtain reason for discontinuation. The physician should document in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

22 Appendix 7 – Research Project 6. Quality of Life and Burden of Disease in TSC

22.1 Research Project Rationale

Most of the studies conducted in TSC have focused on its epidemiology, diagnostic criteria and the efficacy of new treatments, but only a few have evaluated the psychosocial correlates of the illness. Furthermore, the study of families' perspective in caring for a patient with TSC has been neglected so far, even though TSC is mainly diagnosed in childhood and many studies have shown that a child's adaptation to illness and disabilities depends on the family's ability to manage and cope with stress caused by the disease.

Thus a questionnaire to evaluate the impact of TSC on the quality of life of the patients and their families and on the burden of disease is needed.

22.2 Research Objectives

The objective of the questionnaire is t [redacted]

22.3 Research Methods

Patients meeting eligibility criteria for TOSCA will be enrolled in the Research Project upon signature of a project specific informed consent.

Consenting patients or caregivers (for children and disabled patients) will be asked to complete paper questionnaires in the local languages to collect the information on quality of life and burden of illness. The questionnaires are:

- A validated questionnaire to evaluate the quality of life (i.e., EQ5D to be completed by adult patients or EQ5D proxy version 1 to be completed by caregivers)
- A validated questionnaire to evaluate the quality of life in adult patients with epilepsy [Quality of Life in Epilepsy Inventory-31-Problems (QOLIE-31)-P]
- A validated questionnaire to evaluate the quality of life in childhood epilepsy [Quality of Life in Childhood Epilepsy (QOLCE)] for children < 10 years old with epilepsy to be completed by caregivers
- A validated questionnaire to evaluate the quality of life in epilepsy for adolescents [Quality of Life in Epilepsy Inventory for Adolescents-48 (QOLIE-AD-48)] for Adolescents 11-17 years old with epilepsy to be completed by the adolescents themselves (facultative)
- A set of ancillary questions aimed at addressing some specific disease topics (e.g., patient assistance requirements and support/rights, access to healthcare resources, sources of information, clinical trial experience, socio-economic and financial impact, genetic counselling, …)

The ancillary questions were developed in collaboration with the TSC patient associations through the patient representatives involved in the Research Group.

In addition, physicians will be requested to answer to questions on the BOI in the TOSCA registry.The paper questionnaires will be sent from each clinical site to the involved CRO for data entry in the TOSCA registry. Data will then be extracted and analyzed by the involved CRO.

This research project will be run in the European countries involved in TOSCA and interested in participating to this research project.

22.4 Research Project Design

This is a non-interventional, multi-center Research Project conducted in multiple European countries.

In this Research Project no clinical instrumental or laboratory assessments/interventions will be performed other than those required for disease management according to local best practice or required to monitor any treatment as per locally approved summary of product characteristics.

Upon enrollment into the Research Project, patients or their caregivers (for children and disabled patients) will be asked to complete the questionnaires to collect data on QoL and BOI.

22.5 Research Project Completion

Data on QoL and BOI will be recorded once (i.e. no follow up requested) within the end of the collection of data in the TOSCA registry (i.e. 10 August 2017).

22.6 Premature discontinuation

The patients should be followed until the study completion except if any of the following conditions for early termination are met:

- Death
- Lost to follow-up by the site
- Voluntary discontinuation (withdrawal of patients consent to collect or use their data) from the TOSCA disease registry or from the Research Project.

All data generated up to the time of voluntary discontinuation (withdrawal of consent) and the reason(s) for discontinuation will be recorded. Patients who choose to withdraw consent will no longer be contacted for follow up information.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the physician should show “due diligence” by contacting the patients and asking them to return for a final safety assessment. Every effort should be made to obtain reason for discontinuation. The physician should document in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.