

Everolimus Investigator-initiated Protocol Template

RAD001 (Everolimus)

Clinical evaluation of everolimus (a rapamycin analog) in restoring salivary gland function to patients treated with radiotherapy for head and neck cancer

CRAD001XUS274T

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List of abbreviations

4E-BP1	4E-binding protein
AE	Adverse event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area under the curve
BAL	Bronchoalveolar lavage
BCG	Bacillus Calmette-Guérin
CDS	Core data sheet
CoA	Coenzyme A
CPK	Creatine phosphokinase
CRF	Case Report Form
CT	Computer tomography
CTCAE	Common terminology criteria for adverse events
CYP3A4	Cytochrome P450 3A4
DDI	Drug-drug interaction
DLCO	Diffusing capacity of the Lung for Carbon Monoxide
DNA	Deoxyribonucleic acid
DS&E	Drug Safety and Epidemiology
EOT	End of treatment
EU	European Union
FDA	Food and drug administration
GERD	Gastroesophageal reflux disease
HbA1c	Hemoglobin A1c
HBcAb	Hepatitis B core antibody
HbsAb	Hepatitis B surface antibody
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HMG	3-hydroxy-3-methyl-glutaryl
IB	Investigator brochure
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
log ₁₀	Decadic logarithm (common logarithm)
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
NCI	National Cancer Institute
PCR	Polymerase chain reaction
PgP	P-glycoprotein
PFT	Pulmonary function tests

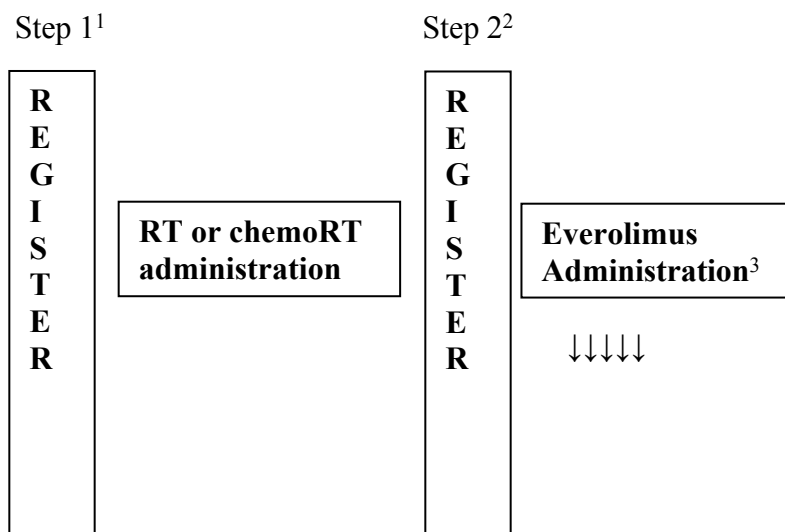
PI3K	Phosphoinositide 3-kinase
PNET	Pancreatic neuroendocrine tumor
RCC	Renal cell carcinoma
RMP	Risk management plan
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SEGA	Subependymal giant cell astrocytoma
TS	Tuberous sclerosis
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
WOCBP	Women of child-bearing potential

Glossary of terms

Assessment	A procedure used to generate data required by the study
Baseline	<p>For efficacy evaluations, the baseline assessment will be the last available assessment before or on the date of randomization.</p> <p>For safety evaluations (i.e. laboratory assessments and vital signs), the baseline assessment will be the last available assessment before or on the start date of study treatment.</p> <p>The value obtained at baseline assessments, referred to as “baseline value” will be used as reference for the patient.</p>
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.

Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

Schema



CORRELATIVE STUDIES⁴

¹ Patients with locally advanced squamous cell carcinoma of the Head and Neck treated with curative intent either in the post-operative or definitive setting with high dose radiotherapy (RT ≥ 50 Gy) with or without chemotherapy (chemoRT) will be eligible

² Verify eligibility for everolimus treatment. Patients with clinically severe gland dysfunction (i.e., those with loss of at least 50% of the pre-radiotherapy value) will be eligible for everolimus treatment.

³ Everolimus (5 or 10 mg) po qd, x 5days only, starting 2 weeks after definitive treatment completion

⁴ Saliva flow rates and xerostomia surveys will be obtained at baseline, after 3 and 6 weeks of RT/chemoRT, prior to everolimus administration, at completion of the 5 day everolimus course and at 1,3 and 6 months after RT/chemoRT completion

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

The clinical symptom of xerostomia (dry mouth syndrome) has been reported as a principle side effect of chronic prescription drug use particularly in the elderly, chemotherapy, therapeutic radiation of the head and neck region, and systemic autoimmune diseases such as Sjögren's syndrome. Approximately 500,000 new patients are diagnosed annually with head and neck cancer worldwide. It is estimated that the tolerance dose for 50% complications rate (TD50) for the parotid gland is 28.4 Gy and the submandibular glands is 39 Gy with the daily dose exposure of <2Gy/day. Regrettably, many surviving patients that received radiotherapy suffer from chronic consequences of oral complications including hyposalivation, increased dental caries, reduced taste and smell, increased risk for oral infections, hampered speech, and malnutrition. Regardless of causal etiology, xerostomia has a significant negative impact on quality of life and presents an elevated financial burden to these individuals.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

Everolimus is a novel derivative of rapamycin. It has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation. Everolimus is approved in Europe and other global markets (trade name: Certican®) for cardiac and renal transplantation, and in the United States (trade name: Zortress®) for the prevention of organ rejection of kidney transplantation.

Afinitor® was approved for adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib in 2009. In 2010, Afinitor® received United States (US) approval for patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC). Everolimus is also available as Votubia® in the European Union (EU) for patients with SEGA associated with TSC who require therapeutic intervention but are not candidates for curative surgical resection. Afinitor® was approved for “progressive pancreatic neuroendocrine tumor (PNET) in patients with unresectable, locally advanced, or metastatic disease” in 2011 in various countries, including the US and Europe. In 2012 Afinitor® received approval for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2- negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole. Furthermore in 2012, Afinitor® received approval for the treatment of patients with TSC who have renal angiomyolipoma not requiring immediate surgery. In the US, Afinitor® was approved in 2016 for advanced non-functional NET of gastrointestinal (GI) or lung origin.

Approximately 44,060 cancer patients (excluding those patients who received marketed Afinitor®, those on planned and roll over studies as well as excluding investigator-sponsored studies) have been treated with everolimus as of 31-Mar-2016:

- 25,356 patients in Novartis-sponsored clinical trials
- 2,043 patients in the individual patient supply program

The following is a brief summary of the main characteristics of Everolimus. More complete information can be obtained from the Everolimus Investigator's Brochure (IB).

1.2.1 Overview of Everolimus

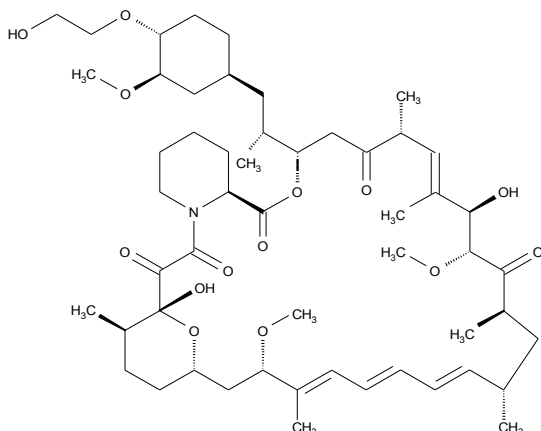
Everolimus is a derivative of rapamycin which acts as a signal transduction inhibitor (Table 1-1, Figure 1-1). Everolimus selectively inhibits mTOR (mammalian target of rapamycin), specifically targeting the mTOR-raptor signal transduction complex. mTOR is a key serine-threonine kinase in the PI3K/AKT signaling cascade, which is known to be dysregulated in a wide spectrum of human cancers (Boulay and Lane 2007).

Everolimus is being investigated as an anticancer agent based on its potential to act

- directly on the tumor cells by inhibiting tumor cell growth and proliferation;
- indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell VEGF (vascular endothelial growth factor) production and VEGF-induced proliferation of endothelial cells).

Table 1-1 Everolimus - Drug substance

Chemical name	(1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12- {(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}- 19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-aza- tricyclo[30.3.1.0 ^{4,9}]hexatriaconta-16,24, 26,28-tetraene-2,3,10,14,20-pentaone
International non-proprietary name	Everolimus

Figure 1-1 Chemical structure of Everolimus

1.2.1.1 mTOR pathway and cancer

At the cellular and molecular level, Everolimus acts as a signal transduction inhibitor. It selectively inhibits mTOR (mammalian target of rapamycin), a key protein kinase which regulates cell growth, proliferation and survival. The mTOR kinase is mainly activated via the phosphatidylinositol 3-kinase (PI3-Kinase) pathway through AKT/PKB and the tuberous sclerosis complex (TSC1/2). Mutations in these components or in PTEN, a negative regulator of PI3-kinase, may result in their dysregulation. Abnormal functioning of various components

of the signaling pathways contributes to the pathophysiology of numerous human cancers. Various preclinical models have confirmed the role of this pathway in tumor development (Cohen et al 2005).

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;
- PI3-kinase mutations have been reported in the primary tumor in 10-20% of human colorectal cancers (Frattoni 2005, Velho 2005);
- The loss of PTEN protein, either through gene deletion or functional silencing (promoter hypermethylation), is reported in approximately 60% of primary human colorectal cancers (Goel et al 2004);
- 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.

1.2.1.2 Non-clinical experience

Everolimus inhibits the proliferation of a range of human tumor cell lines *in vitro* including lines originating from lung, breast, prostate, colon, melanoma and glioblastoma. IC50s range from sub/low nM to μ M. Everolimus also inhibits the proliferation of human umbilical vein endothelial cells (HUVECS) *in vitro*, with particular potency against VEGF-induced proliferation suggesting that Everolimus may also act as an anti-angiogenic agent. The anti-angiogenic activity of Everolimus was confirmed *in vivo*. Everolimus selectively inhibited VEGF-dependent angiogenic response at well tolerated doses. Mice with primary and metastatic tumors treated with Everolimus showed a significant reduction in blood vessel density when compared to controls.

The potential of Everolimus as an anti-cancer agent was shown in rodent models. Everolimus is orally bioavailable, residing longer in tumor tissue than in plasma in a subcutaneous mouse xenograft model, and demonstrating high tumor penetration in a rat pancreatic tumor model. The pharmacokinetic profile of Everolimus indicates sufficient tumor penetration, above that needed to inhibit the proliferation of endothelial cells and tumor cell lines deemed sensitive to Everolimus *in vitro*.

Everolimus administered orally daily was a potent inhibitor of tumor growth, at well tolerated doses, in 11 different mouse xenograft models (including pancreatic, colon, epidermoid, lung and melanoma) and two syngeneic models (rat pancreatic, mouse orthotopic melanoma). These models included tumor lines considered sensitive and “relatively resistant” *in vitro*. In general, Everolimus was better tolerated in mouse xenograft models than standard cytotoxic agents (i.e., doxorubicin and 5-fluorouracil), while possessing similar anti-tumor activity. Additionally, activity in a VEGF-impregnated subcutaneous implant model of angiogenesis and reduced vascularity (vessel density) of Everolimus-treated tumors (murine melanoma) provided evidence of *in vivo* effects of angiogenesis.

It is not clear which molecular determinants predict responsiveness of tumor cells to Everolimus. Molecular analysis has revealed that relative sensitivity to Everolimus *in vitro* correlates with the degree of phosphorylation (activation) of the AKT/PKB protein kinase and the S6 ribosomal protein; in some cases (i.e., glioblastoma) there is also a correlation with PTEN status.

In vivo studies investigating the anti-tumor activity of Everolimus in experimental animal tumor models showed that Everolimus monotherapy typically reduced tumor cell growth rates rather than produced regressions. These effects occurred within the dose range of 2.5 mg to 10 mg/kg, orally once a day.

In preclinical models, the administration of Everolimus is associated with reduction of protein phosphorylation in target proteins downstream of mTOR, notably phosphorylated S6 (p-S6) and p-4E-BP1, and occasionally with an increase in phosphorylated AKT, a protein upstream of mTOR signaling pathway.

All significant adverse events observed in toxicology studies with Everolimus in mice, rats, monkeys and mini-pigs were consistent with its anticipated pharmacological action as an anti-

proliferative and immunosuppressant and at least in part reversible after a 2 or 4-week recovery period with the exception of the changes in male reproductive organs, most notably testes.

In vitro genotoxicity studies covering relevant genotoxicity end-points showed no evidence of clastogenic or mutagenic activity.

In male fertility studies in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count and plasma testosterone levels were diminished at 5 mg/kg which corresponded to 0.7 times the estimated clinical exposure at 10 mg/day, and caused a decrease in male fertility. There was evidence of reversibility. Female fertility was not affected, but everolimus caused an increase of pre-implantation loss in female rats at doses > 0.1 mg/kg, suggesting it could also potentially impact fertility in females. Everolimus crossed the placenta and was toxic to the conceptus. In rats, everolimus caused embryo/fetotoxicity at systemic exposure below the planned therapeutic level comprising mortality and reduced fetal weight. The incidence of skeletal variations and malformations at 0.3 and 0.9 mg/kg (e.g. sternal cleft) was increased. In rabbits, embryo toxicity was evident by an increase in late resorptions. Effects of everolimus on the pre- and postnatal development of rats were limited to slightly affected body weight and survival in the F1-generation at ≥ 0.1 mg/kg, and did not indicate a specific toxic potential.

The potential reproductive risk for humans is unknown. However, due to the observed malformations in rats, everolimus should be considered potentially teratogenic. Everolimus should not be given to pregnant women unless the potential benefit outweighs the potential risk for the fetus. Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving everolimus and up to 8 weeks after treatment has been stopped. It is not known whether everolimus is excreted in human milk. In animal studies, everolimus and/or its metabolites were readily transferred into the milk of lactating rats. Therefore women who are taking everolimus should not breastfeed.

Further details can be found in the Everolimus Investigator's Brochure.

2 Rationale

Limesand and colleagues developed a mouse model to study the effects of salivary gland radiation on glandular functions. Analysis of salivary gland cell proliferation and apoptosis in irradiated mice demonstrated that expression of Akt or treatment with IGF-1 protected irradiated salivary glands; the protective effect of IGF-1 was dependent on autophagy, as evidenced by the lack of protection in IGF-1 treated mice in which Atg5 was conditionally deleted in the salivary gland. Subsequently, Limesand and colleagues showed that mice irradiated with a single dose of radiation (5Gy) and treated with the mTOR inhibitor CCI-779 for five days (experimental days 4-8) had salivary flow rates and amylase secretion similar to unirradiated controls and statistically increased when compared to irradiated mice (Morgan-Bathke 2014). A follow-up mouse pilot study was conducted with a radiation regimen of 2 Gy/day for 5 consecutive days followed by three injections of CCI-779 at four (experimental days 9-11), fourteen (experimental days 22-24) or 30 days (experimental days 38-40) after the last radiation treatment. Preliminary analysis at 60 days post-radiation suggests that **administration of CCI-779 four or fourteen days after radiation leads to improved salivary output** while administration 30 days later did not produce an improvement.

Impact: Reduction in saliva production and oral dryness can have a devastating effect on oral health that potentially leads to malnutrition and poor quality of life. Common palliative therapies for xerostomia include oral lubricants, saliva substitutes, and saliva stimulants (gum, pilocarpine). Unfortunately, these therapies are short-lived and have not consistently demonstrated the ability to relieve xerostomia symptoms. Therefore these patients are left with very few options and this research could provide a long-term solution for these individuals.

This research project brings together a newly-formed, diverse, interdisciplinary team to solve this complex problem. This team takes advantage of the expertise at both Banner – University Medical Center and St. Joseph's Hospital and Medical Center and the ability to recruit patients in Phoenix and Tucson. It extends the mouse model work conducted by the Limesand lab to a phase 0 “proof of principal” clinical trial.

Rapamycin derivatives exhibit considerable similarities in mechanism of action constituting a drug class effect. Therefore, this trial is proposing the use of everolimus due to the ease of administration (orally), which we postulate will have similar biological effects as CCI-779. If successful, the opportunity to expand to a randomized, placebo-controlled, double-blind clinical trial is envisioned.

3 Objectives and endpoints

Initial Objective

Document the safe everolimus dose (5 mg versus 10 mg) to be used in the post radiation or chemoradiation setting for salivary function restoration, using a 3 + 3 design.

Once the safe dose has been defined:

Primary Objective

To describe the recovery of salivary gland function after administration of a 5-day course of everolimus, administered two weeks after completion of radiation or chemoradiation therapy

Primary endpoint

The primary end point of the analysis will be the percent recovery of salivary gland function, with pre-everolimus treatment saliva flow rate as the denominator and the saliva flow rate at 3 months after completion of radiation or chemoradiation therapy as the numerator.

Secondary Objectives

- To describe the decrease of saliva flow rates during radiation or chemoradiation therapy
- To describe the changes in saliva protein composition during radiation or chemoradiation therapy and following administration of a 5-day course of everolimus

Secondary endpoints

Secondary endpoints will be:

- the decrease of saliva flow rates (compared to baseline prior to definitive treatment) during radiotherapy treatment at 3, 6 weeks and prior to everolimus administration and the subsequent recovery of saliva flow rates at completion of the 5 day everolimus course and 1, 3 and 6 months after RT/chemoRT completion to determine the kinetics and stability of saliva flow rate recovery.
- protein composition within the saliva will be measured and will be expressed as percent decrease and recovery of amylase at all available time points.
- Xerostomia Visual Analog Scale survey and Xerostomia Inventory survey will be obtained from each participant at all available time points (See Appendix A and B).

4 Study design

4.1 Description of study design

Patients treated with curative intent either in the post-operative or definitive setting with high dose radiotherapy (≥ 50 Gy) with or without chemotherapy will be eligible. There will be one treatment group with each patient serving as their own control. Patients would have their salivary output measured before radiotherapy, 3 weeks after the start of radiotherapy, and at the end of radiotherapy (6 weeks). Patients who demonstrate more than a 50% decrease in

saliva flow rates will enter the treatment phase of the trial. Based on expert experience, we estimate that half the treated patients will exhibit a decrease of 50% or more in flow rate. These affected patients will then receive the planned dose of everolimus **once a day for 5 days, starting two weeks after the completion of radiotherapy**. Salivary output measurements will be obtained prior to everolimus administration and at completion of the 5 day everolimus course and at 1 month, 3 months and 6 months after the completion of radiation or chemoradiation therapy.

It is our expectation that because of the short exposure to everolimus (a total of 5 days only), the well described everolimus related toxicities will not develop. However, following discussions with the company (Novartis), two dose levels will be evaluated: a starting dose of 5 mg po daily, will initially be evaluated in a cohort of 3 patients.

For the purpose of this trial, dose-limiting toxicity (DLT) is defined as an everolimus-related grade 3 or higher AE.

Toxicity will be graded based on the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

(<http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf>)

As mentioned, we will start treating enrolled patients on the lower dose level.

-If no DLT occurs, will proceed with dose escalation to the full FDA-approved dose (10 mg po daily) [in this case, total number of patients in the trial: 13; 3 in the 5 mg cohort, 10 in the 10 mg cohort] .

-If 1 DLT occurs, cohort will be expanded to additional 3 patients;

and if another DLT occurs in this expanded cohort, no escalation to full dose (10 mg po daily) will be attempted, and cohort will be expanded to 10 patients [in this case, total number of patients in the trial: 10; all in the 5 mg cohort];

and if no additional DLT occurs in the expanded cohort, dose escalation to full dose (10 mg po daily) will follow [in this case, total number of patients in the trial: 16; 6 in the 5 mg cohort, 10 in the 10 mg cohort] .

-If 2 DLT occur, no escalation to full dose (10 mg po daily) will be attempted, and cohort will

be expanded to 10 patients.) [in this case, total number of patients in the trial: 10; all in the 5 mg cohort].

As a result of these possibilities, total number of patients included in this phase 0, proof of principle trial can range from a minimum of 10 to a maximum of 16 total patients.

Maximum number of 16 patients will occur if a DLT occurs in one of the first 3 patients in the 5 mg cohort, and no DLT occurs in the additional 3 expanded cohort patients (for a total of 6 patients in the 5 mg cohort). Subsequently, 10 additional patients will be enrolled in the 10 mg cohort, for a maximum total of 16 patients.

Procedures:

Stimulated Salivary flow measurements:

Patients will undergo both unstimulated whole saliva collection and stimulated whole saliva collection at each visit. Stimulated whole saliva collection measures the ability of the gland to respond to an external stimulus, which is necessary when eating. It is also likely that this measurement will correlate with swallowing difficulties. The average stimulated saliva output for a normal person is 1.5–2.0 mL/min and some studies have used a ≤ 0.5 –0.7 mL/min cutoff for hyposalivation determination.

- Patients must fast overnight, however, they may eat 2 hours prior to their scheduled appointment. They are encouraged to perform oral hygiene immediately after eating their meal to remove any remaining food particles, but no later than the two hour time period before their scheduled appointment. They also need to refrain from smoking two hours prior to their scheduled appointment.
- Saliva production is stimulated by the patient chewing unflavored gum base or paraffin wax (1-2g) for 1 minute. The saliva is then collected by the patient spitting into pre-weighed specimen cups during this time frame

Unstimulated Whole Saliva Flow Rate and Collection

- 1) On the day of saliva collection, patient is to not have eaten for 2 hours prior to their scheduled collection appointment
 - a) No enteral feedings for 2 hours prior to collection appointment
 - b) Patient may eat no later than 2 hours prior to collection appointment; they are encouraged to perform oral hygiene immediately after eating their meal, however, refrain from any additional oral hygiene products 2 hours prior to collection appointment
 - c) Patient must refrain from smoking 2 hours prior to collection appointment
- 2) During the collection period, the patient shall be seated straight up with eyes open and head tilted slightly forward
- 3) The patient will be instructed to minimize oro-facial movements to minimize influence

on salivary flow (the patient should not swallow and should not speak during the collection process).

- 4) Immediately before the collection begins, the patient is instructed to swallow.
- 5) The patient allows the saliva to accumulate on the floor of the mouth for 60 seconds without swallowing.
- 6) The patient empties the entire accumulated saliva into the pre-weighed specimen cup. The procedure is then repeated 2 additional times for a total of 3 minutes. Patients are instructed not to swallow during the entire 5-minute collection period.

Stimulated Whole Saliva Flow Rate and Collection

- 1) On the day of saliva collection, patient is not to have eaten for 2 hours prior to their scheduled collection appointment
 - a) No enteral feedings for 2 hours prior to collection appointment
 - b) Patient may eat no later than 2 hours prior to collection appointment; they are encourage to perform oral hygiene immediately after eating their meal, however, refrain from any additional oral hygiene products 2 hours prior to collection appointment
 - c) Patient must refrain from smoking 2 hour prior to collection appointment
- 2) Patient will chew unflavored sugarless gum for 1 minute (60 seconds).
- 3) Instruct patient to sit motionless.
- 4) Instruct patient to lean their head forward over the specimen cup.
- 5) Instruct patient to swallow to void the mouth of saliva (starting time).
- 6) Every one minute, ask patient to spit saliva into the cup without swallowing. Tell patient “spit out, keep chewing” after first minute, “spit out, keep chewing” after second minute, etc. Discard the first 2-minute collection. A plastic or paper cup may be used for this collection. Proceed with another 3-minute collection. Save this sample for further analysis.
- 7) Ask the patient to spit everything (both saliva and gum base) into the specimen cup.
- 8) Remove the gum base from the specimen cup before weighing the cup with saliva.
- 9) If the patient is too dry, (dry mouth), it is possible to add the weight of the gum base to the pre-weight measure with the gum base in the cup of saliva.

Analysis of saliva: The collection tubes are weighed before and after saliva collection. The difference equates to the total mL collected which is divided by the number of minutes of collection. Saliva is stored at -80°C for further analysis on salivary protein composition at a later date (described in correlatives below).

The comorbidity of mucositis is an important consideration in this study due to the development of this condition following radiotherapy and as a side effect from chronic use of everolimus. Treatment with everolimus has been designed to begin two weeks after radiotherapy to allow radiation-induced mucositis to start improving. In a pre-clinical model,

concurrent rapamycin treatment with radiotherapy (6Gy/day X 5 days) prevents mucositis due in part to increased expression of mitochondrial superoxide dismutase (MnSOD) (Iglesias-Bartolome 2012). Given the short duration of treatment in this trial (5 days), a delay in the start of everolimus until two weeks after radiotherapy and evidence from this pre-clinical study, we postulate that mucositis will not be a major concern. Patients will be closely monitored for worsening mucositis response once treated with everolimus and if mucositis worsens in 2 out of the first 6 patients, then everolimus 50% dose reduction will be implemented.

5 Population

Patients with locally advanced squamous cell carcinoma of the head and neck, treated with curative intent either in the post-operative or definitive setting with high dose radiotherapy (≥ 50 Gy) with or without chemotherapy will be eligible. Patients will be stratified for exploratory analyses in the analysis phase on the basis of ipsilateral vs bilateral neck irradiation. There will be one treatment group with each patient serving as their own control.

This study will evaluate the response in 10 – 16 patients enrolled at both facilities: St. Joseph's Hospital and Medical Center in Phoenix and Banner – University Medical Center in Tucson (details and justification of sample size in statistical methods) to determine if the proposed everolimus dosing schedule of 5 days is sufficient to show recovery of salivary gland function to pre-treatment levels.

These data will also provide guidance on an option for a longer delivery of everolimus in patients with a partial improvement of salivary flow or an option for de-escalation of dose if a large number of patients demonstrate improvements in salivary flow at early time points.

5.1 Inclusion and Exclusion criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

Inclusion criteria:

1. Age 18-75 years
2. Performance status ECOG ≤ 2
3. Adequate bone marrow function as shown by: ANC $\geq 1.5 \times 10^9/L$, Platelets $\geq 100 \times 10^9/L$, Hgb >9 g/dL;
4. Adequate liver function as shown by:
 - a. Total serum bilirubin ≤ 2.0 mg/dL,
 - b. ALT and AST $\leq 2.5 \times$ ULN ($\leq 5 \times$ ULN in patients with liver metastases),
 - c. INR ≤ 2 ;
5. Adequate renal function: serum creatinine $\leq 1.5 \times$ ULN;
6. Fasting serum cholesterol ≤ 300 mg/dL OR ≤ 7.75 mmol/L AND fasting triglycerides $\leq 2.5 \times$ ULN. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication;
7. Signed informed consent obtained prior to any screening procedures.
8. Patients with locally advanced squamous cell carcinoma of the head and neck, treated with curative intent either in the post-operative or definitive setting with high dose radiotherapy (≥ 50 Gy) with or without chemotherapy.

Exclusion criteria:

1. Patients currently receiving anticancer therapies or who have received anticancer therapies within 2 weeks of the start of Everolimus (including chemotherapy, radiation therapy, antibody based therapy, etc.);
2. Known intolerance or hypersensitivity to Everolimus or other rapamycin analogs (e.g. sirolimus, temsirolimus);
3. Known impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral Everolimus;
4. Uncontrolled diabetes mellitus as defined by HbA1c $>8\%$ despite adequate therapy. Patients with a known history of impaired fasting glucose or diabetes mellitus (DM) may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the trial and adjusted as necessary;
5. Patients who have any severe and/or uncontrolled medical conditions such as:
 - a. unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤ 6 months prior to start of Everolimus, serious uncontrolled cardiac arrhythmia, or any other clinically significant cardiac disease
 - b. Symptomatic congestive heart failure of New York heart Association Class III or IV
 - c. active (acute or chronic) or uncontrolled severe infection, liver disease such as cirrhosis, decompensated liver disease, and active and chronic hepatitis (i.e. quantifiable HBV-DNA and/or positive HbsAg, quantifiable HCV-RNA),
 - d. known severely impaired lung function (spirometry and DLCO 50% or less of normal and O₂ saturation 88% or less at rest on room air),
 - e. active, bleeding diathesis;

6. Chronic treatment with corticosteroids or other immunosuppressive agents. Topical or inhaled corticosteroids are allowed;
7. Known history of HIV seropositivity;
8. Patients who have received live attenuated vaccines within 1 week of start of Everolimus and during the study. Patient should also avoid close contact with others who have received live attenuated vaccines. Examples of live attenuated vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines;
9. Patients who have a history of another primary malignancy, with the exceptions of: non-melanoma skin cancer, and carcinoma in situ of the cervix, uteri, or breast from which the patient has been disease free for ≥ 3 years;
10. Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study;
11. Patients who are currently part of or have participated in any clinical investigation with an investigational drug within 1 month prior to dosing;
12. Pregnant or nursing (lactating) women;
13. Women of child-bearing potential (WOCBP) (including female pediatric patients who are menarcheal or who become menarcheal during the treatment), defined as all women physiologically capable of becoming pregnant, must use highly effective methods of contraception during the study and 8 weeks after. Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms). Highly effective contraception methods include combination of any two of the following:

Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate $< 1\%$), for example, hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the oral agent for a minimum of 3 months before taking everolimus

 - a. Total abstinence or;
 - b. Male partner sterilization. (The vasectomized male partner should be the sole partner for that subject)
 - c. Female sterilization have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks prior to randomization. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.
14. Male patients whose sexual partner(s) are WOCBP who are not willing to use adequate contraception, during the study and for 8 weeks after the end of treatment

Screening for hepatitis B

Prior to randomization/start of Everolimus, the following three categories of patients should be tested for hepatitis B viral load and serologic markers, that is, HBV-DNA, HBsAg, HBs Ab, and HBc Ab:

- All patients who currently live in (or have lived in) Asia, Africa, Central and South America, Eastern Europe, Spain, Portugal and Greece.
[<http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/hepatitis-b.htm>]
- Patients with any of the following risk factors:
 - known or suspected past hepatitis B infection,
 - blood transfusion(s) prior to 1990,
 - current or prior IV drug users,
 - current or prior dialysis,
 - household contact with hepatitis B infected patient(s),
 - current or prior high-risk sexual activity,
 - body piercing or tattoos,
 - mother known to have hepatitis B
 - history suggestive of hepatitis B infection, e.g., dark urine, jaundice, right upper quadrant pain.
- Additional patients at the discretion of the investigator

The management guidelines, in Section 6.2.3.10, are provided according to the results of the baseline assessment of viral load and serological markers for hepatitis B.

Screening for hepatitis C

Patients with any of the following risk factors for hepatitis C should be tested using quantitative RNA-PCR:

- known or suspected past hepatitis C infection (including patients with past interferon ‘curative’ treatment),
- blood transfusions prior to 1990,
- current or prior IV drug users,
- current or prior dialysis,
- household contact of hepatitis C infected patient(s),
- current or prior high-risk sexual activity,
- body piercing or tattoos.

At the discretion of the investigator, additional patients may also be tested for hepatitis C.

The management guidelines, in Section 6.2.3.10, are provided according to the results of the baseline assessment of hepatitis C viral load.

6 Treatment

6.1 Study treatment

It is our expectation that because of the short exposure to everolimus (a total of 5 days only), the well described everolimus related toxicities will not develop.

However, following discussions with the company (Novartis), two dose levels will be evaluated: a starting dose of 5 mg po daily, will initially be evaluated in a cohort of 3 patients.

For the purpose of this trial, dose-limiting toxicity (DLT) is defined as an everolimus-related grade 3 or higher AE.

Toxicity will be graded based on the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

(<http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf>)

As mentioned, we will start treating enrolled patients on the lower dose level.

-If no DLT occurs, will proceed with dose escalation to the full FDA-approved dose (10 mg po daily).

-If 1 DLT occurs, cohort will be expanded to additional 3 patients; and if another DLT occurs in this expanded cohort no escalation to full dose (10 mg po daily) will be attempted, and cohort will be expanded to 10 patients. If no additional DLT occurs in the expanded cohort, dose escalation to full dose (10 mg po daily) will follow.

-If 2 DLT occur, no escalation to full dose (10 mg po daily) will be attempted, and cohort will be expanded to 10 patients.

As a result of these possibilities, total number of patients included in this phase 0, proof of principle trial can range from a minimum of 10 to a maximum of 16 total patients.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded.

Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the patient. The storage conditions for Everolimus will be described on the medication label.

Everolimus is supplied by Novartis. Everolimus is formulated as tablets for oral administration of 2.5mg, 5mg, and 10mg strength. Tablets are blister-packed under aluminum foil, which should be opened only at the time of administration as drug is both hygroscopic and light-sensitive. Refer to label for expiration date and storage conditions.

The extent of absorption of everolimus through topical exposure is not known. Therefore,

caregivers are advised to avoid contact with suspensions of Afinitor Tablets. Wash hands thoroughly before and after preparation of either suspension.

6.1.1 Dosing regimen

The investigator should promote compliance by instructing the patient to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

Everolimus should be administered orally once daily at the same time every day, either consistently with or consistently without food.

Tablets

The tablets should be swallowed whole with a glass of water and should not be chewed or crushed. For patients unable to swallow tablets, the tablet(s) should be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring until the tablet(s) is fully disintegrated (approximately 7 minutes), immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse completely swallowed to ensure the entire dose is administered.

If vomiting occurs, no attempt should be made to replace the vomited dose. Patients should be instructed that if they miss a dose on one day, they must not take any extra dose the next day, but instead to immediately contact the study center as soon as possible to ask for advice.

6.2 Dose modifications

6.2.1 Dose modification and dose delay

6.2.1.1 Hepatic impairment dose modifications

Hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumors of gastrointestinal, lung, or pancreatic origin, and advanced renal cell carcinoma:

Severe hepatic impairment (Child-Pugh C) – not recommended. TSC with SEGA

Patients \geq 18 years of age:

- Severe hepatic impairment (Child-Pugh C) – not recommended.

Everolimus whole blood trough concentrations should be assessed approximately 2 weeks after commencing treatment or after any change in hepatic (Child-Pugh) status.

Patients < 18 years of age:

Afinitor is not recommended for patients <18 years of age with TSC who have SEGA and hepatic impairment.

Afinitor is not recommended for patients with hepatic impairment who require doses below 2 mg every other day or 2.5 every other day. Everolimus exposure was increased in patients with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment (see Section 5.2.3). Everolimus is not recommended for use in postmenopausal women with hormone receptor positive advanced breast cancer, or in patients with advanced neuroendocrine tumors of gastrointestinal, lung, or pancreatic origin or advanced renal cell carcinoma with severe hepatic impairment (Child-Pugh C) unless the potential benefit outweighs the risk.

Special Populations

Geriatrics (≥ 65 years) :

No dosage adjustment is required.

Renal impairment :

No dosage adjustment is required.

Ethnicity :

Pharmacokinetic characteristics are similar for Caucasian and Japanese subjects.

Pharmacokinetic studies in Black transplant patients have shown an average 20% higher clearance.

6.2.1.2 Dosing modifications

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are not permitted.

Table 6-1 and Table 6-2 list the dosing guidelines for Everolimus-related non-hematologic and hematologic toxicities.

Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption of Afinitor therapy.

The preceding sections summarize recommendations for dose interruption, or discontinuation of Afinitor in the management of ADRs. General management recommendations are also provided as applicable. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Table 6-1 Dosing guidelines for Everolimus-related non-hematologic toxicities

Toxicity	Action
Non-Infectious Pneumonitis	Discontinue Everolimus.
Reactivation of HBV or HCV flare	Discontinue Everolimus.
AST or ALT elevation Grade 1 (> ULN - 3.0 x ULN) Grade 2 (> 3.0 - 5.0 x ULN)	Maintain current dose level
AST or ALT elevation Grade 3 (> 5.0 - 20.0 ULN)*	Discontinue Everolimus
AST or ALT elevation Grade 4 (> 20 x ULN)*	Discontinue Everolimus
Intolerable grade 2 mucositis, or grade 3 AE, except hyperglycemia or hypertriglyceridemia or hypercholesterolemia (see Section 6.2.3.8)	Discontinue Everolimus
Any other grade 4	Discontinue Everolimus
Grade 3 or 4 clinical liver failure (asterixis or encephalopathy/coma)	Discontinue Everolimus
* Should HCV flare be confirmed, the guidelines for flare must take precedence (Table 6-6)	

Table 6-2 Dosing guidelines for Everolimus-related hematologic toxicities

Toxicity	Action
Grade 2 thrombocytopenia (platelets <75, $\geq 50 \times 10^9/L$)	No action
Grade 3 thrombocytopenia (platelets <50, $\geq 25 \times 10^9/L$)	Discontinue Everolimus
Grade 4 thrombocytopenia (platelets < 25 $\times 10^9/L$)	Discontinue Everolimus
Grade 3 neutropenia or anemia (neutrophil <1, $\geq 0.5 \times 10^9/L$)	Discontinue Everolimus
Grade 4 neutropenia or anemia	Discontinue Everolimus
Febrile neutropenia	Discontinue Everolimus

6.2.2 Management of specific toxicities

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 adverse events (AEs). These AEs are generally reversible and non-cumulative.

Adverse events most frequently observed with everolimus are stomatitis, rash, fatigue, diarrhea, infections, nausea, decreased appetite, anemia, dysgeusia, pneumonitis, edema peripheral, hyperglycemia, asthenia, pruritus, weight decreased, hypercholesterolemia, epistaxis, cough, and headache. Overall, the most frequently observed laboratory abnormalities include decreased hematology parameters including hemoglobin, lymphocytes, platelets, and neutrophils (or collectively as pancytopenia); increased clinical chemistry parameters including cholesterol, triglycerides, glucose, aspartate transaminases, creatinine, alanine transaminases, and bilirubin; and decreased clinical chemistry parameters including phosphate and potassium. The majority of these AEs have been of mild to moderate severity (NCI CTC grade 1-2).

6.2.2.1 Management of infections

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis and viral infections including reactivation of hepatitis B virus, have been described in patients taking Everolimus. Some of these infections have been severe (e.g. leading to sepsis, respiratory or hepatic failure) and occasionally have had a fatal outcome.

Physicians and patients should be aware of the increased risk of infection with Everolimus. Treat pre-existing infections prior to starting treatment with Everolimus. While taking Everolimus, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of Everolimus.

If a diagnosis of invasive systemic fungal infection is made, discontinue Everolimus and treat with appropriate antifungal therapy.

Cases of pneumocystis jirovecii pneumonia (PJP), some with a fatal outcome, have been reported in patients who received everolimus. PJP may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

6.2.2.2 Management of skin toxicity

For patients with grade 1 toxicity, no specific supportive care is usually needed or indicated. Rash must be reported as an AE. Patients with grade 2 or higher toxicity may be treated with the following suggested supportive measures at the discretion of the investigator: oral

minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisolone (short course), topical corticosteroids, or pimecrolimus.

6.2.2.3 Management of Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus.

6.2.2.4 Angioedema with concomitant use of angiotensin-converting enzyme (ACE) inhibitors

Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment).

6.2.2.5 Renal Failure Events

Cases of renal failure (including acute renal failure), some with fatal outcome, occurred in patients treated with everolimus. Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function.

Elevations of serum creatinine, usually mild, and proteinuria have been reported in patients taking everolimus. Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein, or serum creatinine, is recommended prior to the start of everolimus therapy and periodically thereafter.

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6.2.2.6 Management of stomatitis / oral mucositis / mouth ulcers

Adverse Drug Reaction	Severity	Afinitor Dose Adjustment and Management Recommendations
Stomatitis	Grade 1 (Minimal symptoms, normal diet)	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day.
	Grade 2 (Symptomatic but can eat and swallow modified diet)	Temporary dose interruption until recovery to grade ≤ 1 . Re-initiate Afinitor at the same dose. If stomatitis recurs at grade 2, discontinue Afinitor. Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste)*.
	Grade 3 (Symptomatic and unable to adequately eat or hydrate orally)	Discontinue Everolimus
	Grade 4 (Symptoms associated with life-threatening consequences)	Discontinue Afinitor and treat with appropriate medical therapy.

* using agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

Patients with a clinical history of stomatitis/mucositis/mouth ulcers and those with gastrointestinal morbidity associated with mouth/dental infections, irritation of esophageal mucosa e.g. gastroesophageal reflux disease (GERD) and pre-existing stomatitis/mucositis must be monitored even more closely. Patients should be instructed to report the first onset of buccal mucosa irritation/reddening to their study physician immediately.

Stomatitis/oral mucositis/mouth ulcers due to Everolimus should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with Everolimus as mouth ulcers, rather than mucositis or stomatitis. If your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. The suggested paradigm for treatment of stomatitis/oral mucositis/mouth ulcers is as follows:

1. For mild toxicity (grade 1), no dose adjustment required. Manage with non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.
2. For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
3. Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. These agents should be avoided.
4. Antifungal agents should be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of Everolimus metabolism, therefore leading to higher Everolimus exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed.

6.2.2.7 Management of diarrhea

Appearance of grade 1-2 diarrhea attributed to study drug toxicity may be treated with supportive care such as loperamide, initiated at the earliest onset (for example 4 mg orally followed by 2 mg orally every 2 hours until resolution of diarrhea).

6.2.2.8 Management of hyperlipidemia and hyperglycemia

Adverse Drug Reaction	Severity	Afinitor Dose Adjustment and Management Recommendations
Metabolic events (e.g. hyperglycemia, dyslipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.
	Grade 3	Discontinue Everolimus
	Grade 4	Discontinue Everolimus

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits of the patient. Grade 2 or higher hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or grade 2 hypertriglyceridemia or higher (>2.5x upper normal limit) should be treated with a 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g. atorvastatin, pravastatin, fluvastatin) or appropriate triglyceride-lowering medication, in addition to diet.

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine phosphokinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.

Dyslipidemia (including hypercholesterolemia and hypertriglyceridemia) has been reported in patients taking everolimus. Monitoring of blood cholesterol and triglycerides prior to the start of everolimus therapy and periodically thereafter as well as management with appropriate medical therapy is recommended.

Hyperglycemia has been reported in patients taking everolimus. Monitoring of fasting serum glucose is recommended prior to the start of Everolimus and periodically thereafter. More frequent monitoring is recommended when everolimus is co-administered with other drugs that

may induce hyperglycemia. Optimal glycemic control should be achieved before starting a patient on Everolimus.

6.2.2.9 Management of non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking Everolimus. Some of these have been severe and on rare occasions, a fatal outcome was observed.

- A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Opportunistic infections such as PJP should be ruled out in the differential diagnosis of non-infectious pneumonitis. Patients should be advised to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Afinitor therapy without dose alteration.

If symptoms are moderate (grade 2), consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Afinitor may be reintroduced at a daily dose approximately 50% lower than the dose previously administered.

For cases of grade 3 non-infectious pneumonitis, discontinue Afinitor. For cases of grade 4 non-infectious pneumonitis, Afinitor therapy should be discontinued. Corticosteroids may be indicated until clinical symptoms resolve.

For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for pneumocystis jirovecii pneumonia (PJP) may be considered. The two compounds studied most extensively for prophylaxis against PJP have been trimethoprim-sulfamethoxazole, given orally, and pentamidine, given as an aerosol.

If non-infectious pneumonitis develops, the guidelines in Table 6-3 should be followed. Consultation with a pulmonologist is recommended for any case of pneumonitis that develops during the study.

Table 6-3 Management of non-infectious pneumonitis

Worst grade pneumonitis	Suggested investigations	Management of pneumonitis	Everolimus dose adjustment
Grade 1 (Asymptomatic, radiographic findings only)	CT scans with lung windows.	No specific therapy is required	No dose adjustment required. Initiate appropriate monitoring.
Grade 2 (Symptomatic, not interfering with Activities of Daily Living)	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O ₂ saturation at rest. Consider a bronchoscopy with biopsy and/or BAL. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence.	Symptomatic only. Consider corticosteroids and/or other supportive therapy if symptoms are troublesome.	Rule out infection and consider interruption of Everolimus until symptoms improve to Grade ≤ 1.
Grade 3 (Symptomatic, Interfering with Activities of Daily Living. O ₂ indicated)	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O ₂ saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and discontinue Everolimus until symptoms improve to Grade ≤ 1.
Grade 4 (Life-threatening, ventilator support indicated)	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O ₂ saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and discontinue Everolimus.

6.2.2.10 Management of hepatitis reactivation / flare

Reactivation of Hepatitis B (HBV) has been observed in patients with cancer receiving chemotherapy (Yeo 2004). Sporadic cases of Hepatitis B reactivation have also been seen in this setting with everolimus. Use of antivirals during anti-cancer therapy has been shown to reduce the risk of Hepatitis B virus reactivation and associated morbidity and mortality (Loomba 2008). A detailed assessment of Hepatitis B/C medical history and risk factors must be done for all patients at screening, with testing performed prior to the first dose of everolimus.

Monitoring and prophylactic treatment for hepatitis B reactivation

Table 6-4 provides detail of monitoring and prophylactic therapy according to the screening results of viral load and serologic markers testing.

Table 6-4 Action to be taken based on screening hepatitis B results

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-
HBsAb	+ or -	+ or -	+	+ or -	- or + with prior HBV vaccination
HBcAb	+ or -	+ or -	+ or -	+	-
Recommendation	Prophylaxis treatment should be started 1-2 weeks prior to first dose of Everolimus Monitor HBV-DNA approximately every 4-8 weeks		No prophylaxis Monitor HBV-DNA approximately every 3-4 weeks		No specific action

Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of Everolimus. For HBV reactivation definition and management guidelines, see Table 6-5.

Table 6-5 Guidelines for the management of hepatitis B reactivation

HBV reactivation (with or without clinical signs and symptoms)*	
<p>For patients with baseline results: Positive HBV-DNA OR positive HBsAg ----- reactivation is defined as: [Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA]</p>	<p>Treat: Start a second antiviral medication AND Discontinue Everolimus administration.</p>
<p>For patients with baseline results: Negative HBV-DNA and HBsAg AND [Positive HBsAb (with no prior history of vaccination against HBV), OR positive HBcAb] ----- Reactivation is defined as: New appearance of measurable HBV-DNA</p>	<p>Treat : Start first antiviral medication AND Discontinue Everolimus</p>

* All reactivations of HBV are to be recorded as grade 3 (e.g. CTCAE Version 3.0 - Investigations/Other: Viral Reactivation), unless considered life threatening by the investigator, in which case they should be recorded as grade 4. Date of viral reactivation is the date on which the rise or reappearance of HBV-DNA was recorded.

Monitoring for hepatitis C flare

The following two categories of patients should be monitored every 4–8 weeks for HCV flare:

- Patients with detectable HCV RNA-PCR test at screening.
- Patients known to have a history of HCV infection, despite a negative viral load test at screening (including those that were treated and are considered ‘cured’)

For definitions of HCV flare and actions to be taken in the event of a flare, please refer to Table 6-6.

Table 6-6 Guidelines for the management of hepatitis C flare

Baseline results	HCV flare definition*	HCV flare management
Detectable HCV-RNA	> 2 log ₁₀ IU/mL increase in HCV-RNA AND ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Discontinue Everolimus
Knowledge of past hepatitis C infection with no detectable HCV-RNA	New appearance of detectable HCV-RNA AND ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Discontinue Everolimus

* All flares of HCV are to be recorded as grade 3 (e.g. CTCAE Version 3.0 - Investigations - Other: Viral Flare), unless considered life threatening by the investigator; in which case they should be recorded as grade 4. Date of viral flare is the date on which both the clinical criteria described above were met. (e.g., for a patient whose HCV-RNA increased by 2 logs on 01 JAN 2011 and whose ALT reached > 5 x ULN on 22 JAN 2011, the date of viral flare is 22 JAN 2011).

6.3 Concomitant medications

Patients must be instructed not to take any medications (over-the-counter or other products) during the protocol treatment period without prior consultation with the investigator. The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) taken within 28 days of starting study treatment through the 30-day safety follow up visit should be reported on the CRF.

6.3.1 Permitted concomitant therapy

Cytochrome P450 and P-glycoprotein inhibitors/inducers/substrates

Co-administration with strong inhibitors of CYP3A4 or PgP should be avoided; and may cause increased everolimus concentrations. For a current table of Substrates, Inhibitors and Inducers please access the following website:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm>

Everolimus is metabolized by CYP3A4 in the liver and to some extent in the intestinal wall. Therefore, the following are recommended:

- Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) inhibitor should be avoided.
- Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be used with caution. If a patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, reduce the dose of everolimus by approximately 50%. Additional dose reductions to every other day may be required to manage toxicities. If the inhibitor is discontinued, the Everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor after a washout period of 2 to 3 days.
 - **TSC with SEGA:** Everolimus trough concentrations should be assessed approximately 2 weeks after the addition of a moderate CYP3A4/PgP inhibitor. If the inhibitor is discontinued the Afinitor dose should be returned to the dose used prior to initiation of the inhibitor and the everolimus trough concentration should be re-assessed approximately 2 weeks later.
- Grapefruit, Seville oranges, and starfruit affect P450 and PgP activity. Concomitant use should be avoided.
- If patients require co-administration of a strong CYP3A4 inducer, consider doubling the daily dose of Afinitor (based on pharmacokinetic data), using increments of 5 mg or less. This dose of Afinitor is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients.

receiving strong CYP3A4 inducers. If the strong inducer is discontinued, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction), before the Afinitor dose is returned to the dose used prior to initiation of the strong CYP3A4 inducer.

- **TSC with SEGA** Patients receiving concomitant strong CYP3A4 inducers (e.g., the enzyme inducing antiepileptic drugs carbamazepine, phenobarbital, and phenytoin) may require an increased Afinitor dose to attain trough concentrations of 3 to 15 ng/mL. Double the daily dose of Afinitor and assess tolerability. Assess the everolimus trough level two weeks after doubling the dose. Further adjust the dose if necessary to maintain the trough within the 3 to 15 ng/mL range. If the strong inducer is discontinued, the Afinitor dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer and the everolimus trough concentrations should be assessed approximately 2 weeks later.
- This dose adjustment of Everolimus is intended to achieve similar AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the Everolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer.

Please refer to [Table 6-8](#) listing relevant inducers and inhibitors of CYP3A and [Table 6-9](#) for a list of relevant substrates, inducers, and inhibitors of PgP.

Everolimus and drugs influencing CYP3A4 enzyme

Everolimus is a substrate of CYP3A4, and a substrate and moderate inhibitor of the multidrug efflux pump, PgP (PgP, MDR1, and ABCB1). Therefore, extent of absorption and subsequent elimination of systemically absorbed everolimus may be influenced by products that are substrates, inhibitors, or inducers of CYP3A4 and/or PgP. Concurrent treatment with strong CYP3A4-inhibitors should be avoided. Refer to [Table 6-2](#) in section 6 for a comprehensive list of inducers and inhibitors of CYP3A4 and [Table 6-3](#) for a list of relevant substrates, inducers and inhibitors of PgP. Inhibitors of PgP may decrease the efflux of everolimus from brain or tumor and therefore increase everolimus concentrations in these tissues. In vitro studies showed that everolimus is a competitive inhibitor of CYP3A4 and of CYP2D6, potentially increasing the concentrations of products eliminated by these enzymes. Thus, caution should be exercised when co-administering everolimus with CYP3A4 and CYP2D6 substrates with a narrow therapeutic index. Clinical studies have been conducted in healthy subjects to assess pharmacokinetic drug interactions between everolimus and potential CYP3A modifiers (ketoconazole, verapamil, erythromycin, rifampin, midazolam, and HMGCoA reductase inhibitors (statins)).

Table 6-7 Clinically relevant drug interactions: inducers, and inhibitors of isoenzyme CYP3A

Inducers
<p>Strong inducers: avasimibe, carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum)</p> <p>Moderate inducers: bosentan, efavirenz, etravirine, genistein, lersivirine, lopinavir, modafinil, nafcillin, ritonavir, semagacestat, [talviraline], thioridazine, tipranavir</p>

Weak inducers:

amprenavir, aprepitant, armodafinil (R-modafinil), bexarotene, boceprevir, brivacetam, clobazam, danshen, dexamethasone, Echinacea, eslicarbazepine, garlic (allium sativum), ginseng, ginkgo (ginkgo biloba), glycyrrhizin, methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, prednisone, [pleconaril], primidone, quercetin, raltegravir, ritonavir, rufinamide, sorafenib, stribild (combo of elvitegravir, cobicistat, emtricitabine, and tenofovir), sulfapyrazone, telaprevir, terbinafine, ticagrelor, ticlopidine, topiramate, [troglitazone], vemurafenib, vicriviroc/ritonavir, vinblastine

Inhibitors

Strong inhibitors:

boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir / ritonavir, eltegravir/ritonavir, grapefruit juice, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandamycin, voriconazole

Moderate inhibitors:

Amprenavir, aprepitant, atazanavir, atazanavir/ritonavir, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporine, darunavir, darunavir/ritonavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, grapefruit juice (citrus paradisi fruit juice), imatinib, lomitapide, netupitant, nilotinib, schisandra sphenanthera, tofisopam, verapamil

Weak inhibitors:

almorexant, alprazolam, alprazolam, amiodarone, amlodipine, amlodipine, atorvastatin, azithromycin, berberine, bicalutamide, bicalutamide, blueberry juice, cilostazol, cilostazol, cimetidine, clotrimazole, cloxazone, cranberry juice, cyclosporine, delavirdine, everolimus, fluoxetine, fluvoxamine, fosaprepitant, ginkgo, goldenseal, isoniazid, isoniazid, ivacaftor, lacidipine, linagliptin, nilotinib, oral contraceptives, pazopanib, peppermint oil, propiverine, ranitidine, ranitidine, ranolazine, ranolazine, resveratrol, roxithromycin, Seville orange, simeprevir, sitaxentan, tabimorelin, tacrolimus, teriflunomide, ticagrelor, tipranavir/ritonavir, tolvaptan, zileuton

Table 6-8 Clinically relevant drug interactions: substrates, inducers, inhibitors of P-gP and P-gP/CYP3A dual inhibitors

Substrates
afatinib, alfuzosin, aliskiren, alogliptin, ambrisentan, apixaban, apremilast, Aprepitant, atorvastatin acid, atorvastatin, azithromycin, boceprevir, bosentan, carvedilol, caspofungin, ceritinib, cerivastatin, citalopram, colchicine, CP-481,715, cyclosporine, dabigatran, digoxin, docetaxel, domperidone, doxepin, doxorubicin, eribulin, everolimus, fentanyl, fexofenadine, fidaxomicin, fluvastatin, fosamprenavir, gatifloxacin, idelalisib, iloperidone, indacaterol, indinavir, irbesartan, lacosamide, lapatinib, levetiracetam, levofloxacin, linagliptin, linezolid, loperamide, losartan, maraviroc, mirabegron, moxifloxacin, naloxegol, nateglinide, nevirapine, nintedanib, lodaterol, paclitaxel, pantoprazole, paroxetine, pazopanib, phenytoin, posaconazole, pravastatin, proguanil, quinidine, quinine, ranolazine, riociguat, risperidone, ritonavir, rivaroxaban, saquinavir, silodosin, simeprevir, simvastatin, sirolimus, sitagliptin, sofosbuvir, sorafenib, tacrolimus, talinolol, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voclosporin, voriconazole, everolimus
Inducers
avasimibe, carbamazepine, efavirenz, genistein, phenytoin, quercetin, rifampin, St John's wort
P-gP Inhibitors and P-gP/CYP3A Dual Inhibitors
<p>P-gP Inhibitors alogliptin, canagliflozin, cremophor RH40, curcumin, ketoconazole, lapatinib, lopinavir/ritonavir, mirabegron, propafenone, simeprevir, valsopodar, vandetanib, voclosporin</p> <p>P-gP/CYP3A Dual Inhibitors amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fluvoxamine, ginkgo (ginkgo biloba), indinavir, indinavir/ritonavir, itraconazole, mibefradil, milk thistle (silybum marianum), nelfinavir, nifedipine, nitrendipine, paroxetine, quercetin, quinidine, ranolazine, rifampin, ritonavir, saquinavir/ritonavir, Schisandra chinensis, St John's wort (hypericum perforatum), talinolol, Telaprevir, telmisartan, ticagrelor, tipranavir/ritonavir, tolvaptan, verapamil</p>
Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Oct. 2, 2011, 29-Oct-2012 which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies", the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table.

Vaccinations

Immunosuppressants may affect the response to vaccination and vaccination during treatment with Everolimus may therefore be less effective. The use of live vaccines should be avoided during treatment with Everolimus. For pediatric patients with SEGA that do not require immediate treatment, complete the recommended childhood series of live virus vaccinations prior to the start of therapy according to local treatment guidelines. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 Visit evaluation schedule

	Screening / Baseline	RT Day 22	RT Day 43	Post RT day 15	Post RT day 22	Post RT week 6	Post RT week 14	Post RT week 26
Visit no.	1	2	3	4	5	6	7	8
Treatment days*	-21 to -1							
Demography/informed consent (D)	X							
Inclusion/exclusion criteria (D)	X							
Relevant medical history/current medical conditions (D)	X							
Diagnosis and extent of cancer (D)	X							
Prior/post antineoplastic therapy (D)	X							
HIV history (S)	X							
Vital signs (D)	X	X	X	X	X	X	X	X
Height (D)	X							
Weight (D)	X	X	X	X	X	X	X	X
Physical examination (S)	X	X	X	X	X	X	X	X
ECOG performance status (D)	X	X			X	X	X	X
EKG ¹ (D)			X					
Correlative studies	X	X	X	X	X	X	X	X
Hematology ² (D)	X		X	X	X			
Coagulation (D)	X		X	X	X			
Biochemistry ³ (D)	X		X	X	X			
Serum Lipid Profile ⁴ (D)	X		X	X	X			
Prior/concomitant medications (D)	X			X	X			

	Screening / Baseline	RT Day 22	RT Day 43	Post RT day 15	Post RT day 22	Post RT week 6	Post RT week 14	Post RT week 26
Visit no.	1	2	3	4	5	6	7	8
Treatment days*	-21 to -1							
Everolimus ⁵				x				
HBV-DNA, HBsAg, HBs Ab, HBc Ab, HCV- RNA-PCR ⁶ (D)	X							
HBV DNA, HCV RNA-PCR ⁷ (D)	X							

* (+/- 1 day for visits 2,3,4,5; +/- 1 week for visits 6,7,8)

1. Baseline ECG is a standard 12 lead and must be performed within 21 days of first dose for patients enrolled and may be repeated at the investigator's discretion if clinically indicated
2. Hematology tests include a complete blood count (CBC). A total white blood cell (WBC) with absolute differentials (including neutrophil count plus bands, lymphocyte, monocyte, eosinophil, basophil counts), red blood cells (RBC), hemoglobin (Hgb), and a platelet count.
3. Serum Chemistry must include: BUN or uric acid, creatinine, LDH, total protein, electrolytes (sodium, potassium and calcium), total bilirubin, GGT, albumin, alkaline phosphatase, AST/sGOT fasting glucose.
4. Serum fasting lipid profile must include: total cholesterol and triglycerides. Patients should be in fasting state.
5. Everolimus is taken once daily for a total of five days, with drug dispensed at Visit 4.
6. All patients should be screened for hepatitis risk factors and any past illnesses of hepatitis B and hepatitis C. It is highly recommended that patients positive HBV-DNA or HBsAg are treated prophylactically with an antiviral for 1-2 weeks prior to receiving study drug (see Section 6.7.3). The antiviral treatment should continue throughout the entire study period and for at least 4 weeks after the last dose of study drug. Patients with viral hepatitis C risk factors should be screened for HCV RNA-PCR.
7. Patients on antiviral prophylaxis treatment or positive HBV antibodies should be tested for HBV-DNA according to study visit schedule. Patients with positive HCV-RNA PCR or a history of past infection, even if treated and considered 'cured' – should be followed by HCV-RNA PCR according to visit

7.2 Assessment types

7.2.1 Pregnancy and assessments of fertility

There are no adequate data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects including embryo-toxicity and fetotoxicity. The potential risk for humans is unknown. Everolimus should not be given to pregnant women unless the potential benefit outweighs the potential risk to the fetus. If a pregnancy occurs while on study treatment, the newborn will be followed for at least 12 months.

It is not known whether everolimus is excreted in breast milk. However, in animal studies everolimus and/or its metabolites readily passed into the milk of lactating rats. Women taking everolimus should therefore not breast-feed.

Women of childbearing potential

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, (including female pediatric patients who are menarcheal or who become menarcheal during the treatment) must use highly effective contraception during the study and for 8 weeks after stopping treatment. Highly effective contraception is defined as either:

- Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]
- Female Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male partner sterilization: The vasectomized male partner should be the sole partner for that subject with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example, hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the oral agent for a minimum of 3 months before taking everolimus.

Male Contraception

Sexually active males must use a condom during intercourse while taking the drug and for 8 weeks after stopping treatment and should not father a child in this period.

A condom is required to be used also by vasectomised men in order to prevent delivery of the drug via seminal fluid.

Female partners of male patients must also be advised to use one of the following contraception methods: Use of (1) oral, injected, implanted or other hormonal methods of contraception, or (2) intrauterine device (IUD) or intrauterine system (IUS), or (3) prior male/female sterilization.

Fertility

The potential for everolimus to cause infertility in male and female patients is unknown. However, menstrual irregularities, secondary amenorrhea and associated luteinizing hormone (LH)/follicle stimulating hormone (FSH) imbalance has been observed. Based on non-clinical findings, male and female fertility may be compromised by treatment with everolimus.

7.2.2

CORRELATIVES:

The decrease of saliva flow rates (compared to baseline prior to definitive treatment) during radiotherapy treatment at 3, 6 weeks and prior to everolimus administration and the subsequent recovery of saliva flow rates at completion of the 5 day everolimus course and 1, 3 and 6 months after RT/chemoRT completion to determine the kinetics and stability of saliva flow rate recovery.

The production of the saliva protein amylase also decreases with salivary gland dysfunction following irradiation. Hence, we will measure protein composition within the saliva on an Experion microfluidic chip as previously described by the Limesand lab (Grundmann 2010, Morgan-Bathke 2014, Hill 2014).). Briefly, a small amount of saliva (1-2 µl) will be loaded on the Experion microfluidic chips according to manufacturer's instructions. Sample analysis will focus on the profile and concentration of all proteins present in saliva. Percent decrease and recovery of amylase will be measured at all available time points and confirmed using immunoblotting techniques.

Surveys that will administered include:

- a. Xerostomia Inventory survey (Thomson 1999, appendix A)
- b. Xerostomia Visual Analog Scale survey (Pai 2001, appendix B)

8 Safety monitoring and reporting

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy

(e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded *in the Adverse Events CRF*. Conditions that were already present at the time of informed consent should be recorded *in the Medical History page of the patient's CRF*. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event. Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. *Its duration (Start and end dates) (add or Ongoing at End of Study for)*
3. *Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) or
Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)*
4. *Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)*
5. *Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)*
6. *Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met*

Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown) If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Any AE that constitutes a DLT will be reported like a grade 3 and 4 adverse event.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

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 study treatment, the interventions required to treat it, and the outcome.

Any and all adverse events will be recorded on the UACC adverse events record form and reviewed by the Principal Investigator.

NOTE : This only applies to non-interventional trials. All non-serious AEs suspected to be causally related to the Novartis drug of focus i.e. ADRs must be periodically transferred to Novartis.

Adverse Drug Reactions

Oncology

The most common ADRs, suspected to be related to treatment by the investigator (incidence $\geq 1/10$) from the pooled safety data were (in decreasing order): stomatitis, rash, fatigue, diarrhea, infections, nausea, decreased appetite, anemia, dysgeusia, pneumonitis, edema peripheral, hyperglycemia, asthenia, pruritus, weight decreased, pruritus, asthenia, peripheral edema, hypercholesterolemia, epistaxis, cough and headache.

The most common grade 3/4 ADRs, suspected to be related to treatment by the investigator (incidence $\geq 1/100$ to $< 1/10$) were stomatitis, anemia, hyperglycemia, fatigue, infections, pneumonitis, diarrhea, asthenia, thrombocytopenia, neutropenia, dyspnea, lymphopenia, proteinuria, hemorrhage, hypophosphatemia, rash, hypertension, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, and pneumonia and diabetes mellitus.

The below table presents the frequency category of ADRs reported in the pooled safety analysis.

ADRs are listed according to MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse reaction: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$)

Infections and infestations

Very common - Infections_a

Blood and lymphatic system disorders

Very common - Anemia,

Common - Thrombocytopenia, neutropenia, leukopenia, lymphopenia

Uncommon - Pancytopenia

Rare - Pure red cell aplasia

Immune system disorders

Uncommon - Hypersensitivity

Metabolism and nutrition disorders

Very common - Decreased appetite, hyperglycemia, hypercholesterolemia

Common - Hypertriglyceridemia, hypophosphatemia, diabetes mellitus, hyperlipidemia, hypokalemia, dehydration

Psychiatric disorders

Common - Insomnia

Nervous system disorders

Very common - Dysgeusia, headache

Uncommon - Ageusia

Cardiac disorders

Uncommon - Congestive cardiac failure

Vascular disorders

Common - Hemorrhage^b, hypertension,

Uncommon - Deep vein thrombosis

Respiratory, thoracic and mediastinal disorders

Very common - Pneumonitis^c, epistaxis, cough,

Common - dyspnea

Uncommon - Hemoptysis, pulmonary embolism

Rare - , acute respiratory distress syndrome

Gastrointestinal disorders

Very common - Stomatitis^d, diarrhea, nausea

Common - Vomiting, dry mouth, abdominal pain, oral pain, dyspepsia, dysphagia

Skin and subcutaneous tissue disorders

Very common - Rash, pruritus

Common - Dry skin, nail disorder, acne, erythema, hand-foot syndrome

Rare - Angioedema

Musculoskeletal and connective tissue disorders

Common - Arthralgia

Renal and urinary disorders

Common - Proteinuria, Renal failure

Uncommon - Increased daytime urination, acute renal failure

Reproductive system and breast disorders

Common - Menstruation irregular ^f

Uncommon -, amenorrhea

General disorders and administration site conditions

Very common - Fatigue, asthenia, edema peripheral, ,

Common - Pyrexia, mucosal inflammation

Uncommon - Non-cardiac chest pain, impaired wound healing

Investigations

Very common - Weight decreased

Common - aspartate aminotransferase increased, Alanine aminotransferase increased, blood creatinine increased

^a Includes all reactions within the 'infections and infestations' system organ class including common: pneumonia, urinary tract infection and uncommon: bronchitis, herpes zoster, sepsis, abscess and isolated cases of opportunistic infections (e.g. aspergillosis,

and rare : viral myocarditis
candidiasis and hepatitis B)

^b Includes different bleeding events from different sites not listed individually

^c Includes common: pneumonitis: interstitial lung disease, lung infiltration, and rare - alveolitis, pulmonary alveolar hemorrhage, and pulmonary toxicity

^d Includes very common: stomatitis; common: aphthous stomatitis, mouth and tongue ulceration; uncommon: glossitis, glossodynia

^e reported as palmar-plantar erythrodysesthesia syndrome

^f frequency is based upon number of women age 10 to 55 years of age in the safety population

Clinically relevant laboratory abnormalities

In the pooled double-blind phase III safety database, the following new or worsening clinically relevant laboratory abnormalities were reported with an incidence of $\geq 1/10$ (very common, listed in decreasing frequency).

- Hematology: hemoglobin decreased, lymphocytes decreased, white blood cells decreased, platelets decreased, and neutrophils decreased (or collectively as pancytopenia);
- Clinical chemistry: glucose (fasting) increased, cholesterol increased, triglycerides increased, AST increased, phosphate decreased, ALT increased, creatinine increased, potassium decreased, and albumin decreased.

Most of the observed abnormalities ($\geq 1/100$) were mild (grade 1) or moderate (grade 2). Grade 3/4 hematology and chemistry abnormalities include:

- Hematology: lymphocytes decreased, hemoglobin decreased, (very common); neutrophils decreased, platelet count decreased, white blood cells decreased (all common).
- Clinical chemistry: glucose (fasting) increased, phosphate decreased, potassium decreased, AST increased, ALT increased, creatinine increased, cholesterol (total) increased, triglycerides increased, albumin decreased (all common).

Tuberous sclerosis complex (TSC)

The most frequent ADRs (incidence $\geq 1/10$ and suspected to be related to treatment by the investigator) from the pooled safety database are (in decreasing order): stomatitis, upper respiratory tract infections, amenorrhea, hypercholesterolemia, nasopharyngitis, acne, menstruation irregular, sinusitis, and pneumonia

The most frequent grade 3/4 adverse reactions (incidence $\geq 1/100$ to $< 1/10$ and suspected to be related to treatment by the investigator) were stomatitis, amenorrhea, pneumonia, neutropenia, pyrexia, and gastroenteritis viral.

The below table shows the incidence of ADRs based on pooled data in patients receiving everolimus in the TSC studies (including both the double-blind and open-label study and extension periods). ADRs are listed according to MedDRA system organ class. Frequency categories are defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data). Within each frequency grouping, ADRs are presented in order of decreasing frequency.

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



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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, 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 - menorrhagia, 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, tongue 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 while on treatment in the safety pool

Clinically relevant laboratory abnormalities

In the pooled TSC safety database the following new or worsening clinically relevant laboratory abnormalities reported with an incidence of $\geq 1/10$ (very common, listed in decreasing frequency):

- Hematology: partial thromboplastin time increased, hemoglobin decreased, white blood cells decreased, neutrophils decreased, lymphocytes decreased, and platelet count decreased.
- Clinical chemistry: cholesterol increased, triglycerides increased, AST increased, ALT increased, phosphate decreased, alkaline phosphatase increased, potassium decreased, and glucose (fasting) increased.

Most of the laboratory abnormalities were mild (grade 1) or moderate (grade 2). Grade 3/4 hematology and chemistry abnormalities included:

- Hematology: neutrophils decreased, partial thromboplastin time increased (common) and lymphocytes decreased, hemoglobin decreased (uncommon).
- Clinical chemistry: phosphate decreased, alkaline phosphatase increased, AST increased (common); cholesterol increased, triglycerides increased, ALT increased, potassium decreased, and glucose (fasting) increased (uncommon).

Description of selected adverse drug reactions

In clinical trials and post-marketing spontaneous reports, everolimus has been associated with serious cases of the following :

- hepatitis B reactivation, including fatal outcome. Reactivation of infections is an expected event during periods of immunosuppression.
- renal failure events (including fatal ones) and proteinuria. Monitoring of renal function is recommended.
- amenorrhea (including secondary amenorrhea).
- Pneumocystis jirovecii pneumonia (PJP) some with a fatal outcome.
- Angioedema has been reported with and without concomitant use of everolimus and ACE inhibitors

The table below lists all fatal adverse events reported by investigators across all RAD001 studies as having a suspected causal relationship to everolimus and occurring on or before the cut off date of 31-Mar-2014.

MedDRA system organ class	Event
Blood and lymphatic system disorders	Thrombocytopenia
Cardiac disorders	Acute cardiopulmonary event, cardiogenic shock, cardio-respiratory arrest, myocardial infarction
Gastrointestinal disorders	Diarrhea, duodenal ulcer, GI hemorrhage, intestinal perforation, esophageal perforation, internal hernia
General disorders/administration site conditions	Cold sweat, concomitant disease progression, general physical health deterioration, multi-organ failure, sudden death
Infections and infestations	Candidal sepsis, EBV pneumonia, neutropenic sepsis, pneumocystis jirovecii pneumonia, Reactivation of

	Hepatitis B, septic shock, septicemia with massive Epstein-Barr viremia
Injury, poisoning and procedural complications	Bone fissure
Metabolism and nutrition disorders	Dehydration, ketoacidosis, hyperglycemia
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Squamous cell carcinoma of skin
Nervous system disorders	Cerebral hemorrhage, embolic stroke, restlessness
Renal and urinary disorders	Renal tubular necrosis
Respiratory thoracic and mediastinal disorders	Acute cardiopulmonary event, acute respiratory distress syndrome, cardio-respiratory arrest, dyspnea, chronic obstructive pulmonary disease, interstitial pneumonia, pulmonary embolism, pulmonary edema, pneumonitis
Vascular Disorders	Cerebral hemorrhage, disseminated intravascular coagulation, embolic stroke, hemorrhage, hypovolemic shock, myocardial infarction, pulmonary hypertension

The table below lists all serious, unexpected, life-threatening adverse events considered related to study drug, and reported on

at least one occasion up to the cut-off date of 31-Mar-2014. It should be stressed that many of these SAE reports have been reported only on a single occasion making an accurate

assessment of causality difficult, if not impossible. Due to the imprecision of causality, the causality assessments should not be assumed that all of these events are indeed the result of therapy with everolimus. Moreover, the assessment of causality is particularly difficult in critically ill patients where confounding factors are present relating mainly to complications of the underlying disease and to the use of prior therapy and/or concomitant medications. In addition to the SAE reports presented below, disease progression has on occasions been reported somewhat paradoxically as an SAE with a suspected causal relationship to everolimus and reported on at least one occasion.

Individual events are presented for each MedDRA system organ class.

MedDRA system organ class	Event
Blood and lymphatic system disorders	Acute leukemia, anemia, bone marrow failure, disseminated intravascular coagulation, febrile neutropenia , hemorrhagic diathesis, leukemoid reaction, leukocytosis, leukopenia, lymphadenopathy, lymphedema, lymphopenia, neutropenia, pancytopenia, platelet disorder, retroperitoneal lymphadenopathy, thrombocytopenia, white blood cell disorder, hemolytic uremic syndrome
Cardiac disorders	atrial fibrillation, atrioventricular block, ardiorespiratory arrest , cardiopulmonary arrest, congestive cardiomyopathy, cyanosis, diastolic dysfunction, dilatation left atrial and left ventricular, hypertrophy, left ventricular hypertrophy, left ventricular dysfunction , myocardial infarction, myocardial ischemia, hypertensive heart disease, palpitations, pericardial effusion, right ventricular failure, sinus tachycardia, stress cardiopathy, supraventricular tachycardia, tachycardia, ventricular dysfunction Valve incompetence: mitral/pulmonary/tricuspid
Ear and labyrinth disorders	Vertigo, sudden hearing loss, deafness unilateral
Endocrine disorders	Hyperthyroidism, hyperglycemic non-ketotic syndrome, hypercalcemia, hypothyroidism

Eye disorders	Conjunctivitis, eyelid edema, scleral discoloration, ocular discomfort, ocular surface disease, phthalmoplegia_cranial nerve paralysis, papilloedema, photophobia, retinal artery thrombosis, retinal detachment, retinal hemorrhage, steroid Induced cataract, senile cataract, visual acuity reduced.
Gastrointestinal disorders	Abdominal abscess, abdominal adhesions, abdominal: discomfort/distension/pain/tenderness, anorectal discomfort, anal fissure, anal fistula, anastomotic leak, ascites, colitis, constipation, diarrhea, diverticulum, duodenal ulcer, dyspepsia, dysphagia, esophageal perforation, feces discolored, gastric perforation, gastric ulcer hemorrhage, gastric ulceration, gastrointestinal angiodysplasia, gastrointestinal ischemia, gastrointestinal oedema, gastroenteritis , hemorrhoids, hematemesis, hematochezia, hiccups, ileus, intestinal perforation, melena, mesenteric vein thrombosis, mouth ulceration, nausea, pancreatitis, proctalgia, proctitis, recall phenomenon radiation enteritis, rectal discharge/hemorrhage, small intestinal obstruction, stomatitis, swollen tongue, vomiting, oral pain, enterovesical fistula, radiation esophagitis, necrotizing esophagitis, salivary gland calculus, small bowel thickness, thickened bowel Wall Gastritis: erosive/ hemorrhagic Lip: edema/swelling/ulceration Gastrointestinal: disorder/hemorrhage/sounds Mucosal: hemorrhage/inflammation
General disorders and administration site conditions	Application site erythema, asthenia, bloody discharge, calcinosis, chest discomfort/pain, chills, concomitant disease progression, condition aggravated, crepitations, death, discomfort, disease progression, drug ineffective, and drug withdrawal syndrome (asthenia and flushing) edema peripheral, face edema, facial pain, fatigue, feeling of body temperature change, general physical health deterioration, generalized edema, goiter , granuloma, hypertrophy, hypothermia, impaired healing, inflammation, influenza like illness, irritability, local swelling, malaise, mass, multi-organ failure, necrosis, non-cardiac chest pain, pain, performance status decreased, pitting edema, pyrexia, sudden death, swelling, tenderness, thirst
Hepatobiliary disorders	Cholecystitis, cholelithiasis, cholestasis, cytolytic hepatitis, hepatic cirrhosis, hepatic failure , hepatic function abnormal, hepatic necrosis, hepatorenal failure , hepatitis B and C reactivation, hepatomegaly, hyperbilirubinemia, jaundice, portal vein thrombosis
Immune system disorders	Acute disseminated encephalomyelitis, autoimmune disorder, cytokine release syndrome, Guillian Barre syndrome, hypersensitivity, immunosuppression, Stevens-Johnson syndrome
Infections and infestations	Bronchitis, bronchopneumonia, bronchopulmonary aspergillosis. candida sepsis, cellulitis, citrobacter sepsis, clostridium bacteremia, endocarditis, escherichia bacteremia, folliculitis, gastroenteritis, hepatitis fulminant. infected lymphocele, klebsiella sepsis, liver abscess, meningitis, herpes, nasopharyngitis, neutropenic sepsis, perirectal/anal abscess, pharyngitis, pneumococcal sepsis, pseudomonal bacteremia, purulent discharge, pyelonephritis, respiratory moniliasis, sepsis syndrome, septic shock, sinusitis, staphylococcal bacteremia, staphylococcal sepsis, streptococcal bacteremia, tonsillitis, tuberculosis, urosepsis Infection(s): alpha hemolytic streptococcal/atypical mycobacterial/bacterial/clostridial/enterobacter/enterococcal/epstein-barr virus/ escherichia/escherichia urinary tract/gastrointestinal/haemophilus/herpesvirus/ general/ localized/ morganella/ proteus/ skin/streptococcal/staphylococcal/urinary tract/ wound staphylococcal
Injury, poisoning and Procedural complications	Abdominal adhesion, anastomotic leak, bone fissure, collapse of lung, contusion, eschar, fall, head injury, lung injury, medical device complication, medication error, post procedural swelling, recall phenomenon radiation enteritis, surgical procedure repeated, vena cava injury, wound dehiscence/secretion
Investigations	Aspiration pleural cavity, antinuclear antibody positive, bleeding time prolonged, breath sounds abnormal, cardiac function test abnormal, chest X-ray abnormal, clostridium difficile toxin test positive, computerised tomogram abnormal, ejection fraction decreased, endoscopy upper gastrointestinal tract, general physical condition abnormal, granulocyte count decreased, hematocrit/hemoglobin decreased, hypophosphatemia, liver function test abnormal, neutrophil count

	<p>abnormal/decreased, occult blood positive, oxygen saturation abnormal/decreased, peak expiratory flow rate decreased, protein urine present, QRS axis abnormal, urine output decreased, X-ray abnormal; Increased: alanine aminotransferase, ammonia, aspartate aminotransferase, aspartate aminotransferase, body temperature, C-reactive protein, eosinophil count, gamma-glutamyltransferase, international normalised ratio, lipase, red blood cell count, sedimentation rate, transaminases, troponin T, troponin Platelet count: abnormal/decreased/increased White blood cell(s): count abnormal/decreased/in urine Lymphocyte count: decreased/increased Blood: amylase increased/albumin decreased/alkaline phosphatase increased/bilirubin increased/creatinine phosphokinase increased/creatinine increased/magnesium decreased/glucose increased/lactate dehydrogenase increased/potassium decreased/pressure diastolic decreased/pressure orthostatic abnormal/pressure systolic decreased/triglycerides increased/urea increased/urine present Electrocardiogram: T wave abnormal/T wave amplitude decreased/poor R-wave progression Weight: decreased/ increased</p>
Metabolism and nutrition disorders	<p>Acidosis, anorexia, appetite disorder, cachexia, cushing's syndrome, decreased appetite, dehydration, diabetes mellitus, diabetic ketoacidosis, electrolyte imbalance, failure to thrive, fluid overload/retention, food intolerance, glucose tolerance impaired, gout, hypothyroidism, malnutrition, metabolic acidosis, oral intake reduced, polydipsia, type 2 diabetes mellitus Hyper: cholesterolemia/glycemia/kalemia/lipidemia/calcaemia uricemia/ triglyceridemia, glycaemic non-ketotic syndrome Hypo: calcemia/glycemia/kalemia/magnesiumemia/natremia/ proteinemia/ hypophosphatemia</p>
Musculoskeletal and connective tissue disorders	<p>Arthritis, bone fissure, fistula, gout mobility decreased, joint effusion, rhabdomyolysis Pain: back/flank/musculoskeletal/musculoskeletal chest/extremity/neck Muscle: spasms/weakness; myalgia, arthralgia Osteoarthritis; Osteonecrosis, Osteoreadionecrosis</p>
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	<p>Acute leukemia, adenocarcinoma of pancreas, Burkitt's lymphoma, carcinoid syndrome, colon neoplasm, lung neoplasm, lymphoproliferative disorder, malignant neoplasm progression, malignant melanoma, malignant pleural effusion, pancreatic carcinoma, squamous cell carcinoma of skin, uterine leiomyoma Metastases: central nervous system/lung/lymph nodes/neoplasm; Tumor: hemorrhage/necrosis</p>
Nervous system disorders	<p>Acute disseminated encephalomyelitis, asterixis, ataxia, cerebrovascular accident, cognitive disorder, complex partial seizures, complex regional pain syndrome, convulsion, depressed level of consciousness, dizziness, dyslalia, encephalitis, encephalopathy, facial palsy, headache, hemiparesis, hemiplegia, hyperglycemic non-ketotic syndrome, hypersomnia, hypoglycemic coma, lethargy, loss of consciousness, ophthalmoplegia_cranial nerve paralysis, neuralgia, neuropathy peripheral, presyncope, sinus headache, somnolence, speech disorder, tremor, vertigo Cerebral: hemorrhage/ infarction/ischemia; transient ischemic attack</p>
Psychiatric disorders	<p>Agitated depression, anxiety, confusional state, delirium, delusional disorder, disorientation, drug withdrawal syndrome, libido decreased insomnia, mental disorder/status changes, mood altered, persecutory type, personality disorder, neurosis, staring</p>
Renal and urinary disorders	<p>Acute renal failure, anuria, bladder tamponade, dysuria, hematuria, hemolytic uremic syndrome, hydronephrosis, leukocyturia, nephrolithiasis, oliguria, pollakiuria, polyuria, postrenal failure, renal failure/acute/impairment, urinary bladder hemorrhage, urinary incontinence, renal atrophy, renal colic, renal tubular necrosis</p>
Reproductive/breast disorders	<p>Azospemia, endometrial hyperplasia, libido decreased, menorrhagia, pelvic pain, ovarian cyst, scrotal edema</p>
Respiratory, thoracic and mediastinal disorders	<p>Alveolitis, alveolitis allergic, asthma, atelectasis, bronchomalacia, bronchospasm, cough, cryptogenic organizing pneumonia, diffuse alveolar damage, dysphonia, dyspnea/dyspnea exertional, emphysema, epistaxis, hemoptysis, hydrothorax, hypercapnia, hypoxia, laryngeal edema, interstitial lung disease, laryngeal inflammation, pneumothorax, rales, sinus congestion, stridor, tachypnea, wheezing Acute: respiratory distress syndrome/respiratory failure Lung: consolidation/disorder/infiltration, obstructive airways disorder, orthopnoea, pharyngolaryngeal pain, pleural disorder/effusion/pleurisy/pain; pneumonia aspiration, pneumonitis, pneumothorax, pro</p>

	Pulmonary: congestion/alveolar/hemorrhage/artery dilatation/cavitation/embolism/fibrosis/haemorrhage/hypertension/edema/toxicity Respiratory: arrest/disorder/distress/failure/gas exchange disorder
Skin and subcutaneous tissue disorders	Acute febrile neutrophilic dermatosis, Angioedema, blister, dermatitis, dermatitis acneiform, erythema, hyperhidrosis, leukocytoclastic vasculitis, night sweats, petechiae, photosensitivity reaction, pruritus, Stevens-Johnson syndrome Rash: erythematous/generalized/ maculo-papular/pruritic/skin disorder/exfoliation/lesion/reaction/ulcer/palmar plantar erythrodysesthesia/hand foot syndrome
Surgical and medical procedures	Abscess drainage, biliary drainage, bladder irrigation, catheter removal, chest tube insertion, cholecystectomy, debridement, endotracheal intubation, fistula repair, gastric ulcer surgery, gastrointestinal tube insertion, ileojejunal bypass, incisional drainage, laparotomy, mechanical ventilation, pleurodesis, sinus operation, surgery, thoracic cavity drainage, tracheostomy Pericardial: drainage/excision/operation Wound: closure/drainage/treatment
Vascular disorders	Capillary leak syndrome, circulatory collapse, embolism, flushing, gastrointestinal angiodysplasia, gastrointestinal ischaemia, haemorrhoids, hematoma, hemodynamic instability, hemorrhage, hypertension, hypertensive angiopathy, hypertensive crisis, hypotension, lymphangiopathy, lymphedema, pallor, shock; transient ischemic attack, retinal hemorrhage, Thrombosis: deep vein/jugular vein

*New events added to IB Editions 12 and 13 are noted in bold

8.1.2 Laboratory test abnormalities

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol and is still, by definition, an adverse event.

8.2 Serious Adverse Events

8.2.1 Definitions

A serious adverse event is an undesirable sign, symptom or medical condition 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 the studied indication, not associated with any deterioration in condition (specify what this includes)
 - 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 study drug
 - 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
 - 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

8.2.2 Reporting

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E) (*For patients taking Novartis drugs*).

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment/participation must be reported to Novartis within 24 hours of learning of its occurrence. Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and **send the completed, signed form along with the Novartis provided fax cover sheet to the Novartis Oncology Drug Safety and Epidemiology (DS&E) department by fax (fax: 877-778-9739) within 24 hours.**

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Everolimus Investigator Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a DS&E associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees

in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

All serious adverse events and any deaths will be reported to the DSMB and to the University of Arizona Human Subjects Protection Program per the guidelines set forth in University of Arizona Cancer Center Data and Safety Monitoring Board Charter, Table 5: Adverse Event Reporting.

All submitted serious adverse events will be processed by the DSMB Coordinator monthly for initial trend analysis and then reviewed by the DSMB Chair. The assigned QA/QC Monitor will review the SAE reporting process to confirm reporting requirements are met.

8.3 Pregnancy

To ensure patient safety, each pregnancy occurring while the patient is on study treatment 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 reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E) by fax (**fax : 877-778-9739**). Pregnancy follow-up should include an assessment of the possible relationship to the investigational/study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

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

9 Statistical methods

9.1 Statistical methods

All patients will have their salivary output measured before radiotherapy, 3 weeks after the start of radiotherapy, and at the end of radiotherapy (6 weeks). Patients with clinically severe gland dysfunction (i.e., those with loss of at least 50% of the pre-radiotherapy value) will be eligible for everolimus treatment. Follow-up measurements will be obtained prior to everolimus administration, at completion of the 5 day everolimus course at 1 month, 3 months and 6 months after RT/chemoRT completion.

The primary end point of the analysis will be the percent recovery of salivary gland function, with pre-everolimus treatment saliva flow rate as the denominator and the saliva flow rate at 3 months after completion of radiation or chemoradiation therapy as the numerator.

It is our expectation that because of the short exposure to everolimus (a total of 5 days only), the well described everolimus related toxicities will not develop.

However, following discussions with the company (Novartis), two dose levels will be evaluated: a starting dose of 5 mg po daily, will initially be evaluated in a cohort of 3 patients.

For the purpose of this trial, dose-limiting toxicity (DLT) is defined as an everolimus-related grade 3 or higher AE.

Toxicity will be graded based on the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

(<http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf>)

As mentioned, we will start treating enrolled patients on the lower dose level.

-If no DLT occurs, will proceed with dose escalation to the full FDA-approved dose (10 mg po daily) [in this case, total number of patients in the trial: 13; 3 in the 5 mg cohort, 10 in the 10 mg cohort] .

-If 1 DLT occurs, cohort will be expanded to additional 3 patients;

and if another DLT occurs in this expanded cohort, no escalation to full dose (10 mg po daily) will be attempted, and cohort will be expanded to 10 patients [in this case, total number of patients in the trial: 10; all in the 5 mg cohort];

and if no additional DLT occurs in the expanded cohort, dose escalation to full dose (10 mg po daily) will follow [in this case, total number of patients in the trial: 16; 6 in the 5 mg cohort, in the 10 mg cohort] .

-If 2 DLT occur, no escalation to full dose (10 mg po daily) will be attempted, and cohort will be expanded to 10 patients.) [in this case, total number of patients in the trial: 10; all in the 5 mg cohort].

As a result of these possibilities, total number of patients included in this phase 0, proof of principle trial can range from a minimum of 10 to a maximum of 16 total patients.

Maximum number of 16 patients will occur if a DLT occurs in one of the first 3 patients in the 5 mg cohort, and no DLT occurs in the additional 3 expanded cohort patients (for a total of 6 patients in the 5 mg cohort). Subsequently, 10 additional patients will be enrolled in the 10 mg cohort, for a maximum total of 16 patients.

Planned analyses will be performed by strata (patients enrolled at the 5 mg dose level versus the 10 mg dose level).

Statistical analysis will compute the mean percent recovery of all treated patients (with a 95% confidence interval). Ten patients at the selected dose will allow estimating the mean percent recovery with standard error that is 0.32 of the observed standard deviation. Exploratory analysis will determine if any clinical factors are predictive of treatment response, specifically ipsilateral vs bilateral neck irradiation. Changes in the secondary endpoints across time, including the saliva flow rates, saliva protein composition, total score obtained on the Xerostomia Inventory survey, and total score on the Xerostomia Visual Analog Scale survey, will be explored using graphical methods.

10 Protocol amendments, or changes in study conduct

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed by Novartis and the investigator before implementation.

Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A copy of the written approval of the IRB must be provided to Novartis. Examples of amendments requiring such approval are:

1. increases in drug dose or duration of exposure of subjects,
2. significant changes in the study design (e.g. addition or deletion of a control group),
3. increases in the number of invasive procedures,
4. addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Novartis in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Novartis must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

1. changes in the staff used to monitor trials
2. minor changes in the packaging or labeling of study drug.

11. Data and Safety Monitoring Plan

11.1 Identification of the DSMB obligated for oversight responsibilities:

The University of Arizona Cancer Center Data and Safety Monitoring Board (DSMB) will provide ongoing oversight for this trial. This study has been assigned a High Risk level by the DSMB.

11.2 Identification of the entity obligated for routine monitoring duties:

Routine monitoring will be provided by The University of Arizona Cancer Center Quality Assurance/Quality Control (QA/QC) Program to ensure that the investigation is conducted according to protocol design and regulatory requirements.

Data from each subject visit will be entered into the OnCore system within 1 week of the subject visit.

This trial will also undergo real-time monitoring by the PI and study team, including documentation of real-time monitoring of any new or ongoing safety issues. Weekly conference calls will be conducted with PI and study staff to address the following:

- adverse events (including serious adverse events):

- screening and enrollment including cohort management.
- protocol deviations and corrective action plans for any identified deviations
- accuracy and timeliness of data collection/entry

11.3 **Monitoring progress and data review process:**

Routine monitoring of subject data will be conducted at least every month.

The first routine monitoring visit will include at a minimum:

- Informed consent – 100% of cases enrolled;
- Subject eligibility – 100% of cases, up to three subjects;
- Data review – 100% of cases, up to three subjects.

All subsequent monitoring visits will consist of randomly selected subject cases based on current enrollment and include continuing review of previously selected cases, as applicable.

A monitoring visit report and follow-up letter will be completed approximately two weeks after the routine monitoring visit; a copy will be maintained in the study file. The monitor will request additional source documentation, clarification, information, or corrections to the CRF and/or regulatory records from the Clinical Research Coordinator (CRC) or other applicable staff responsible for the study and resolution of queries/findings. Documentation of such a request will be maintained with a copy of the monitor's visit report for follow-up at the next monitoring visit. Electronic records will be available in the institutional database or provided by the QA/QC Program staff.

The Principal Investigator will ensure the accuracy, completeness, legibility and timeliness of the data reported in the Case Report Form (CRF), or other acceptable data formats. Source documentation supporting the study data should indicate the subject's participation in the trial and should document the dates and details of study procedures, adverse events, and patient status.

All Case Report Forms (CRF) will be entered into the institutional database and completed electronically.

Note: Routine monitoring of regulatory documents will be conducted at least every six months, and routine monitoring of test article will be conducted at least every three months.

11.4 **Process to implement study closure when significant risks or benefits are identified:**

Please see section 9.1 for escalation and de-escalation procedure which may include study closure as determined by occurrence of dose limiting toxicities.

11.5 Plan for assuring data accuracy and protocol compliance:

Routine study activity and safety information will be reported to the DSMB on a monthly basis, or more frequently if requested. These reports will include:

- Study activity, cumulative and for the period under review;
- Safety (narrative description on non-serious and serious adverse events, protocol pre-determined early stopping rules for safety or treatment-emergent adverse events);
- Predetermined protocol early stopping rules for efficacy/futility;
- Status of study in relationship to stopping rules;
- Current dose level of study agent;
- Routine monitoring and protocol compliance (describe the monitoring process and identify the status of the monitoring);
- Comments;
- Attachments (AE data reviewed by the PI to compile the report, SAE letters and reports, results of any review(s), applicable correspondence with the IRB or other regulatory agencies).

Data, safety and study progress will be reported to:

- Human Subjects Protection Program (IRB) at least annually;

11.6 Identification of the sponsor or funding agency, as applicable:

The PI will immediately notify, in writing, Novartis, if applicable, any action resulting in a temporary or permanent suspension of the study. A copy of this correspondence will also be forwarded to the DSMB and the SRC.

11 References:

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Appendix A: The Xerostomia Inventory (Thomson 1999)

1.	I sip liquids to aid in swallowing food				
	1	2	3	4	5
	Never	Hardly ever	Occasionally	Fairly often	Very often
2.	My mouth feels dry when eating a meal				
	1	2	3	4	5
	Never	Hardly ever	Occasionally	Fairly often	Very often
3.	I get up at night to drink				
	1	2	3	4	5
	Never	Hardly ever	Occasionally	Fairly often	Very often
4.	My mouth feels dry				
	1	2	3	4	5
	Never	Hardly ever	Occasionally	Fairly often	Very often
5.	I have difficulty in eating dry foods				
	1	2	3	4	5
	Never	Hardly ever	Occasionally	Fairly often	Very often
6.	I suck sweets or cough lollies to relieve dry mouth				
	1	2	3	4	5
	Never	Hardly ever	Occasionally	Fairly often	Very often
7.	I have difficulties swallowing certain foods				
	1	2	3	4	5
	Never	Hardly ever	Occasionally	Fairly often	Very often
8.	The skin on my face feels dry				
	1	2	3	4	5
	Never	Hardly ever	Occasionally	Fairly often	Very often
9.	The skin on my face feels dry				
	1	2	3	4	5
	Never	Hardly ever	Occasionally	Fairly often	Very often
10.	My lips feel dry				
	1	2	3	4	5
	Never	Hardly ever	Occasionally	Fairly often	Very often
11.	The inside of my nose feels dry				
	1	2	3	4	5
	Never	Hardly ever	Occasionally	Fairly often	Very often

Appendix B: Visual Analog Scale (VAS) Xerostomia Questionnaire (Pai 2001)

1. Rate the difficulty you experience in speaking due to dryness

Not difficult at all Very difficult

2. Rate the difficulty you experience swallowing due to dryness

Not difficult at all Very difficult

3. Rate how much saliva is in your mouth

A lot None

4. Rate the dryness of your mouth

Not dry at all Very dry

5. Rate the dryness of your throat

Not dry at all Very dry

6. Rate the dryness of your lips

Not dry at all Very dry

7. Rate the dryness of your tongue

Not dry at all Very dry

8. Rate the level of your thirst

Not thirsty at all Very thirsty