EUROPEAN UNION RISK MANAGEMENT PLAN

Systemic Tacrolimus (Prograf™, Prograft™, Advagraf™, Modigraf™)

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EU Risk Management Plan for (Prograf™ Prograft™, Advagraf™, Modigraf™) (Tacrolimus Monohydrate)

Risk Management Plan (RMP) version to be assessed as part of this application:

RMP Version number:	5.2
Data lock point for this RMP:	22 Feb 2024
Date of final sign-off:	26 Jun 2024

Rationale for submitting an updated RMP:	Update of milestone of the final report planned date of the feasibility assessment of conducting an NI-PASS of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from available secondary use data sources to replicate the TPRI study. To add data sources from Denmark and France as additional secondary-use data sources to the design of feasibility assessment.
Summary of significant changes in this RMP:	In this RMP updates were made to Part III.2, Part III.3, Part VI.II.C and Annex 2, in order to add data sources from Denmark and France as additional secondary-use data sources to the design of feasibility assessment, and to correct the milestone related to the final report planned date of the feasibility assessment of conducting an NI-PASS of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from available secondary use data sources to replicate the TPRI study. The safety concerns have not changed in this version.

Other RMP versions under evaluation:

RMP Version Number(s)	Submitted on	Procedure Number(s)
5.0	30 Jun 2023	EMEA/H/C/WS2519

Details of the currently approved RMP for Systemic tacrolimus:	
Version number:	4.0
Approved with procedure:	EMEA/H/C/WS2402
Date of approval (opinion date)	26 Apr 2023

QPPV approval/oversight:

QPPV name: Ralph Nies, M.D.

QPPV signature: Electronic signature appended at the end of the document

List of Abbreviations

Abbreviation	Definition
AE	Adverse Events
ADR	Adverse Drug Reaction
ATC	Anatomical therapeutic chemical classification
AUC	Area under the curve
CAV	Chronic Allograft Vasculopathy
CHMP	Committee for medicinal products for human use
CHO	Chinese hamster ovary cell
CI	Confidence Interval
COMMIT	Consensus on Managing Modifiable Risk in Transplantation
CPG	Clinical Practice Guidelines
CTD	Common Technical Document
CVD	Cardiovascular Disease
CYP3A4	Cytochrome P-450 3A4 isoenzyme
DHPC	Direct healthcare professional communication
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GI	Gastrointestinal
GP	General practitioner
HCP	Healthcare Professionals
HGPRT	Hypoxanthine-Guanine Phosphoribosyl-Transferase
HLGT	High Level Group Term
IFN	Interferon
INN	International Nonproprietary Name
JC	John Cunningham
MAH	Marketing authorization holder
MPA	Mycophenolic Acid
MedDRA	Medical Dictionary for Regulatory Activities
NI-PASS	Non-Interventional Post-Authorization Safety Study
PAM	Post-authorization measures
PCR	Polymerase Chain Reaction

PK	Pharmacokinetics
PL	Package Leaflet
pmp	Per Million Population
PRAC	Pharmacovigilance Risk Assessment Committee
PRCA	Pure Red Cell Aplasia
PRES	Posterior Reversible Encephalopathy Syndrome
PSUR	Periodic Safety Update Report
PT	Preferred Term
RMP	Risk Management Plan
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SOT	Solid Organ Transplant
TdP	Torsade de Pointes
TPRI	Transplant Pregnancy Registry International
UK	United Kingdom
UV	Ultraviolet
VCA	Viral Capsid Antigen

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PART I: PRODUCT(S) OVERVIEW

Data-lock point for this Module	31 Dec 2019
Version when Module last updated	3.0

Table Part I.1: Product Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Tacrolimus monohydrate
Pharmacotherapeutic group(s) (ATC Code)	L04AD02 Calcineurin inhibitors
Name of Marketing Authorization Holder (MAH) or Applicant	Astellas Pharma Europe B.V (on behalf of all EEA Astellas MAHs).
Medicinal products to which this RMP refers	4
Invented name(s) in the European Economic Area (EEA)	Tacrolimus Immediate Release Hard Capsules (Prograf™, Prograft™) (0.5, 1, 5 mg) Tacrolimus Prolonged Release Capsules (Advagraf™) (0.5, 1, 3, 5 mg) Tacrolimus Granules for Oral Suspension (Modigraf™) (0.2, 1 mg) Tacrolimus Concentrate for Solution for Infusion (5mg/mL) (Prograf™, Prograft™ Concentrate for Solution for Infusion) (Note: Prograf and Prograft are different trade names used for same medicinal product in different countries. Therefore, Prograf and Prograft will be further referred to as Prograf in this report).
Marketing authorization procedure	Advagraf and Modigraf: Centralized procedure Prograf capsules and concentrate for solution for infusion: Mutual recognition procedure and National procedures

Brief description of the product	Chemical class Tacrolimus is a macrolide lactone fermentation product of *Streptomyces tsukubaensis*, and an established immunosuppressive agent belonging to the pharmacological class of calcineurin inhibitors.
	Summary of mode of action The key pharmacodynamic action of tacrolimus is inhibition of cytokine gene transcription. Tacrolimus suppresses T-cell activation, and the formation of cytotoxic lymphocytes which are mainly responsible for the rejection of transplanted organs and T-helper cell dependent B-cell proliferation.
	Important information about its composition Prograf Capsules is the immediate-release formulation of systemic tacrolimus, for twice daily oral administration. Advagraf is the prolonged-release formulation of systemic tacrolimus, for once daily oral administration. Modigraf is the granule formulation of systemic tacrolimus for mixing with water as an oral suspension, for twice daily administration. Prograf Concentrate for Solution for Infusion is a concentrate for solution containing systemic tacrolimus, for intravenous infusion, for use only after it is diluted with suitable carrier media.
Hyperlink to the product information	Module 1.3.1
Indication(s) in the EEA	Current: Prograf Capsules: - Prophylaxis of transplant rejection in liver, kidney, or heart allograft recipients; - Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products. Advagraf: - Prophylaxis of transplant rejection in adult kidney or liver allograft recipients; - Treatment of allograft rejection, resistant to treatment with other immunosuppressive medicinal products, in adult patients. Modigraf: - Prophylaxis of transplant rejection in adult and pediatric kidney, liver, or heart allograft recipients; - Treatment of allograft rejection, resistant to treatment with other immunosuppressive medicinal products in adult and pediatric patients.
Indication(s) in the EEA (*continued*)	Prograf Concentrate for Solution for Infusion: - Prophylaxis of transplant rejection in liver, kidney or heart allograft recipients; - Treatment of allograft rejection, resistant to treatment with other immunosuppressive medicinal products.
Dosage in the EEA	Current:

	General considerations: The recommended initial dosages are intended to act solely as a guideline. Tacrolimus dosing should primarily be based on clinical assessments of rejection and tolerability, in each patient individually, aided by blood level monitoring. Brief overview of the dosing advice: for extensive dosing advice refer to the individual SmPC(s): Prograf Capsules and Modigraf dosage recommendations – **Liver transplantation** Prophylaxis of transplant rejection - **adults** Initial oral dose 0.10 - 0.20 mg/kg/day, administered as two divided doses. Prophylaxis of transplant rejection - **children** Initial oral dose 0.30 mg/kg/day administered in 2 divided doses. - **Kidney transplantation** Prophylaxis of transplant rejection – **adults** Initial dose 0.20 - 0.30 mg/kg/day, administered as 2 divided doses. Prophylaxis of transplant rejection – **children** Initial oral dose of 0.30 mg/kg/day, administered in 2 divided doses. - **Heart transplantation** Prophylaxis of transplant rejection – **adults** Initial dose of 0.075 mg/kg/day, administered as 2 divided doses. Prophylaxis of transplant rejection – **children** In patients without antibody induction: Initial oral dose 0.30 mg/kg/day. Following antibody induction: Initial oral dose 0.10 - 0.30 mg/kg/day, administered as two divided doses. Advagraf dosage recommendations – **Liver transplantation** Initial oral dose 0.10 - 0.20 mg/kg/day administered once daily in the morning.
Dosage in the EEA (*continued*)	– **Kidney transplantation** Initial oral dose 0.20 - 0.30 mg/kg/day administered once daily in the morning. - **Heart transplantation** In adult patients converted to Advagraf, an initial oral dose of 0.15 mg/kg/day should be administered once daily in the morning. Prograf Concentrate for Solution for Infusion – **Liver transplantation** Prophylaxis of transplant rejection - **adults** Intravenous therapy of 0.01 - 0.05 mg/kg/day, initiated as a continuous

	24-hour infusion. Prophylaxis of transplant rejection - **children** Initial intravenous dose of 0.05 mg/kg/day, administered as a continuous 24-hour infusion. **- Kidney transplantation** Prophylaxis of transplant rejection – **adults** Intravenous therapy of 0.05 - 0.10 mg/kg/day, initiated as a continuous 24-hour infusion. Prophylaxis of transplant rejection – **children** Initial intravenous dose of 0.075 – 0.100 mg/kg/day, administered as a continuous 24-hour infusion. Dose adjustment during post-transplant period in adults and children: Tacrolimus doses are usually reduced in the post-transplant period. **Rejection therapy** – **adults and children** Increased tacrolimus doses have been used to manage rejection episodes. If signs of toxicity are noted, the dose of tacrolimus may need to be reduced.
Pharmaceutical form(s) and strengths	Current: Prograf 0.5, 1, and 5 mg, immediate-release hard capsules: each capsule contains tacrolimus monohydrate corresponding to 0.5, 1, and 5 mg tacrolimus respectively. Advagraf 0.5, 1, 3 and 5 mg, prolonged-release hard capsules: each capsule contains tacrolimus monohydrate corresponding to 0.5, 1, 3, and 5 mg tacrolimus respectively. Modigraf 0.2 mg and 1 mg granules for oral suspension: each sachet contains tacrolimus monohydrate corresponding to 0.2 mg and 1 mg tacrolimus respectively. Prograf Concentrate for Solution for Infusion contains 5 mg of tacrolimus in 1 mL concentrate solution for infusion.
Is/will the product be subject to additional monitoring in the EU?	No

ATC: Anatomical Therapeutic Chemical Classification; EEA: European Economic Area; INN: International Nonproprietary Name; MAH: Marketing Authorization Holder; RMP: Risk Management Plan

PART II: SAFETY SPECIFICATION

PART II: MODULE SI. EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Data-lock point for this Module	31 Dec 2019
Version when Module last updated	3.0

Indication

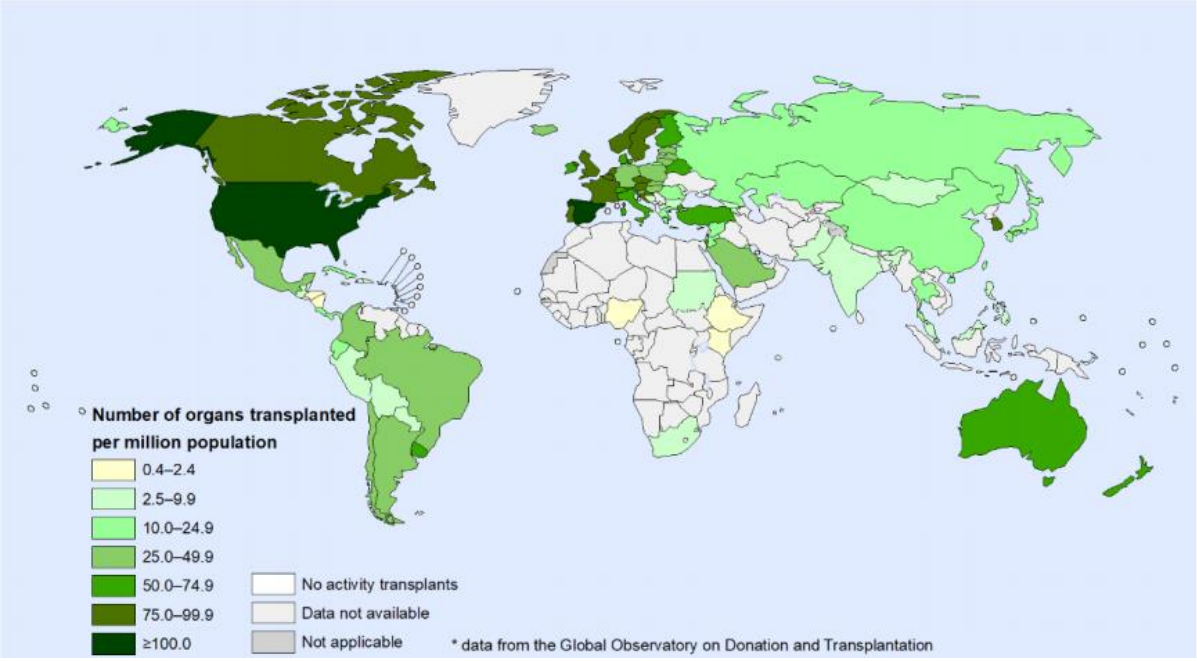
Tacrolimus is indicated for the prophylaxis of liver, kidney and heart transplant (prophylaxis of heart transplant is only indicated for Prograf and Modigraf) and for the treatment of allograft rejection, and in patients unresponsive to treatment with other immunosuppressive medicinal products.

SI.1 Epidemiology of the disease

Incidence, prevalence and demographic profile of target population

In 2017, 139,000 solid organ transplants (SOTs) were performed globally. Kidney transplantation represents 65% of all SOT procedures, followed by liver transplantation (23%), heart transplantation (6%), lung transplantation (4%), and pancreas transplantation (2%) [GODT, 2017].

Figure 1. Global transplantation activities of solid organs, 2017 [GODT, 2017]



In 2017, 34,000 SOTs were performed in the 28 European Union (EU) countries. Kidney was the most transplanted organ (62%) followed by the liver (23%), heart (6%), lung (6%), pancreas (2%), and small bowel transplantation (1%). The number of SOTs performed in the EU varies from 1.8 procedures per million population (pmp) in Bulgaria to 28.3 pmp in Croatia [Newsletter transplant, 2018].

In 2016, there were 7,741 pediatric SOTs in the EU countries. Kidney was the most transplanted organ in pediatric transplant recipients (43.2%) followed by the liver (39.1%), heart (12.3%), lung (4.2%), and multivisceral (1.2%) [European Reference Network, 2018].

SI.2 Epidemiology of liver transplant

Incidence

In the EU, 7,984 liver transplants were performed in 2017, equivalent to 15.7 procedures pmp. Among these, 3% were from living donors [Newsletter transplant, 2018]. Croatia had the highest rate (31.7 pmp) of liver transplants in 2018. This was an increase from 2017 in Croatia when the rate was 28.3 per million. Belgium followed with the second highest rate in 2018 at 26.8 liver transplants per million. Austria had the largest increase (apart from Croatia) between 2017 and 2018, from 18.5 to 20.7 pmp [Stewart, 2019].

Demographics of the targeted population

The pediatric liver transplant population represents 10% of the total liver transplants in Europe [Adam et al, 2018]. In Europe, the average age of liver transplantation in adult recipients has increased steadily over the last 15 years, with a 16% increase in the number of liver transplant recipients aged 65 years or more between 2012 and 2016 [Durand et al, 2019].

A 2018 annual report from the European Liver Transplant Registry presented data without stratification by age or gender [Adam et al, 2018]. An annual report on liver transplantation in the United Kingdom (UK), among pediatric transplant recipients, showed that 52% were female and 38% were aged 1-4 years [Hopkinson and Taylor, 2018]. Evidence from the UK Liver Transplant Audit (UKLTA) of adults, linked to the Hospital Episode Statistics database (1997-2010), showed that the majority of liver transplant recipients were male (62.6%) and Caucasian (87.3%), followed by Asian (9.4%) and Black (2.3%) [Tovikkai et al, 2015].

Risk factors for End Stage Liver Disease

Cirrhosis is the most frequent indication for liver transplant in Europe and is mainly related to either viral infection (hepatitis C virus or hepatitis B virus) or alcohol abuse [Adam et al, 2018]. Cirrhosis is followed by three major indications: primary liver tumors, cholestatic liver disease and acute hepatic failure. Other diseases that are indicated in liver transplant include biliary atresia, metabolic diseases, Wilson's disease, α1-antitrypsin deficiency, familiar amyloidotic polyneuropathy, Budd-Chiari, benign liver tumor, and secondary liver tumor [Adam et al, 2018].

The main indications for liver transplant are distributed differently according to the age of recipients. Biliary atresia and metabolic diseases are reported as the major indications in pediatric patients (≤18 years), and cirrhosis with end-stage liver disease and cancer are the major indications in adults.

Natural history in the population, including mortality and morbidity

Dayoub et al. reported donor age was an independent predictor of graft failure following liver transplantation [Dayoub et al, 2018]. The critical period, for post liver transplant outcome, is

the first year; 46% of deaths and 67% of re-liver transplants occur within the first year after liver transplant [Adam et al, 2018].

Survival rates of liver transplant recipients have been reported as 83% at 1 year, 71% at 5 years, 61% at 10 years, 51% at 15 years and 41% at 20 years [Adam et al, 2018]. The 5-year patient survival was better for cirrhosis (71%) than for primary liver tumors (64%) or acute hepatic failure (65%). Pediatric liver transplant recipients have shown a better 5-year survival rate (90%) than adults (81%). In addition, age has been associated with survival in adult recipients. Survival rates have been found to be 75% for adults aged 18-45, 71% for those aged 46-60, 65% for adults aged 61-70, and 60% for those over 70 years [Adam et al, 2018].

Although 5-year survival has improved in the 2000s and 2010s for all indications, the most important gains were observed among those with liver transplants for primary liver tumors (67%), liver metastases (61%), and acute liver failure (69%). The main causes of death after primary liver transplantation include primary graft non-function or dysfunction, infections and technical complications (biliary or vascular) [Adam et al, 2018].

Main existing treatment options

The commonly used immunosuppressive agents during liver transplantation are prednisolone, tacrolimus, cyclosporine, mycophenolate mofetil, mycophenolic acid sodium, azathioprine, sirolimus, everolimus, Muromonab-CD3, alemtuzumab, daclizumab and basiliximab [Moini et al, 2015].

Important co-morbidities

The most frequent co-morbidities associated with liver transplant recipients were diabetes mellitus, hypertension, cardiovascular diseases (CVDs) (myocardial infarction, peripheral vascular disease, cerebrovascular disease), chronic pulmonary disease, chronic renal disease and creatinine >1.5 mg/dL [Asrani, et al, 2018; Tovikkai et al, 2015].

SI.3 Epidemiology of Kidney Transplant

Incidence

In the EU, 21,100 kidney transplants were performed in 2017, equivalent to 41.7 procedures pmp [Newsletter transplant, 2018]. Amongst these, 20% were from living donors. Spain had the highest rate (71.4 pmp) of kidney transplant procedures in 2018. This was a slight increase from 2017, when the rate was 70.5 per million. The Netherlands followed, in 2018 with the second highest rate at 58.4 kidney transplants per million. Estonia had the largest rate increase between 2017 and 2018, from 26.9 to 44.6 pmp [Stewart, 2019].

Demographics of the targeted population

The proportion of renal transplants among children, in Europe, has been reported at around 4.6% [Saeed, 2012]. In children, renal transplants were more frequent in recipients aged 12-19 years [Dipchand et al, 2013]. In adults, the age distribution of kidney transplant

recipients has been reported to be similar for both sexes, with 39% of procedures performed in recipients aged 45-64 years [Kramer et al, 2019].

Risk factors for End Stage Renal Disease

Chronic kidney disease is the most common indication for renal transplant in Europe. Renal transplant recipients remain at an increased risk of fatal and non-fatal cardiovascular events, as compared to the general population. The major indications for renal transplant in infants are structural abnormalities of the urinary tract, congenital nephrotic syndrome, polycystic diseases, and neonatal kidney injury [Jalanko et al, 2016].

In adults, CVD is the leading indication for renal transplant recipients [Devine et al, 2019].

Natural history in the population, including mortality and morbidity

In comparison to their age-matched peers, renal transplant recipients display a 3 to 5-fold increased risk of CVD [Kasiske et al, 2004]. Kidney transplant recipients have a high prevalence of pre-existing, as well as de novo, traditional CVD risk factors, such as hypertension (40–90%) [Premasathian et al, 2004; Kasiske et al, 2003], diabetes (24–42%) [Badiou et al, 2009], dyslipidemia (50%) [Kasiske and Klinger, 2000], and smoking (25%) [Kidney Disease, 2009]. Non-traditional risk factors include adverse metabolic effects of immunosuppression, chronic anemia, hyperhomocysteinemia, chronic inflammation, proteinuria and chronic allograft nephropathy [Rangaswami et al, 2019]. It is recognized that morbidity and mortality from CVD is not entirely accounted for by the aforementioned non-traditional risk factors. The overall CVD risk in renal transplant recipients is likely to be multifactorial and a complex interaction between the multiple traditional and non-traditional factors [Neale and Smith, 2015].

Graft survival has been shown to vary according to the recipient's age. Chesnaye et al, investigated the impact of the donor age in pediatric kidney transplantation using data from European Renal Association - European Dialysis and Transplant Association. Their study showed that in recipients 0-5 years of age, the 5- and 10-year graft survival rates were 84.2% (95% confidence interval [CI] 81.5–86.6) and 75.2% (95% CI 71.7–78.4) [Chesnaye et al, 2017], respectively. In the subgroup of patients transplanted at 0-3 years of age, the 5- and 10-year graft survival rates were 83.8% (95% CI 80.0–87.0) and 76.7% (95% CI 71.9–80.8). In the recipient aged 6–11 years, the 5- and 10-year graft survival rates were 89.9% (95% CI 87.9–91.5) and 76.7% (95% CI 73.4–79.6), and in recipients aged 12-19 years, the 5-year graft survival was 84.6% (95% CI 82.8–86.3) [Premasathian et al, 2004]. In another study by Coemans et al, it was observed that the age of the recipient was inversely related to the hazard of graft failure. Younger patients were more inclined to graft failure after transplantation than older patients. The effect of recipient age was no longer seen after the age of 55 [Coemans et al, 2018].

Main existing treatment options

The commonly used immunosuppressive agents during kidney transplantation are azathioprine, prednisolone, cyclosporine, antithymocyte globulin, antilymphocyte globulin, thymoglobulin, mycophenolate mofetil, basiliximab, daclizumab, tacrolimus, sirolimus, everolimus, rituximab and alemtuzumab [Muntean and Lucan, 2013].

Important co-morbidities

The most common co-morbidities associated with kidney transplant recipients are diabetes, pulmonary disease, acute myocardial infarction, peripheral vascular disease and connective tissue disorder [Pieloch et al, 2014; Begaj et al, 2013].

SI.4 Epidemiology of heart transplant

Incidence

In the EU, 2,169 heart transplants were performed in 2017, equivalent to 4.3 procedures pmp [Newsletter transplant, 2018]. Slovenia had the highest rate of heart transplants in 2018, at 11.0 pmp. Croatia followed in 2018, with the second highest rate at 8.8 heart transplants per million. Bulgaria had the lowest heart transplant rate at 0.6 procedures per million in 2018 [Stewart, 2019].

Demographics of the targeted population

Pediatric heart transplantation represents 14% of all cardiac transplantations, according to the registry of the International Society of Heart and Lung Transplantation. Infant heart transplantation (children below 1 year of age) represents 24% of all pediatric heart transplantations [Dipchand et al, 2015]. Almost every fourth heart organ donor in Europe (23.2%) is 50 years of age or older [Stehlik et al, 2011]. The proportion of adult donors allocated to pediatric recipients is as high as 43% in Europe [Dipchand et al, 2013].

In Europe, the median donor age for heart recipients of all ages has continued to increase and reached 42 years in 2010. The proportion of donors ≥50 years of age has been reported at 27% in Europe. Allografts from donors ≥60 years of age are used sparsely - only 2% of all donors, in 2010, were in this age group. For adult heart transplantation, hearts from older donors are more often transplanted into older recipients [Stehlik et al, 2012].

Women undergo cardiac transplantation less frequently than men, a trend that has persisted for decades, with less than a third of heart organs being allocated to women [Frankenstein et al, 2012]. Recent literature suggests a number of contributing factors for gender disparities in cardiac transplantation, including fewer women being listed for a transplant, more women dying while waiting on the transplant list, less aggressive heart failure treatment in women, and an increased sensitization in women, limiting the donor pool from which a match can be found [Kenchaiah and Vasan, 2015; Joseph, 2015 ; Frankenstein et al, 2012].

Risk factors for End Stage Heart Disease

Cardiovascular factors such as diabetes mellitus, hypertension, obesity, history of ischemic heart disease and prior thoracic surgery have been indicated in heart transplantation [Almenar et al, 2005]. Congenital heart disease is one of the most common indications for heart transplantation in children, especially in infants in whom it represents approximately 54% of all heart transplantations. Heart transplantation in those with adult congenital heart disease presents many unique challenges because these patients tend to have cumulative risk factors such as multiple prior surgeries, long-standing cardiac dysfunction or cyanosis with effects on other organs (i.e., kidneys, liver, lungs), and elevated pulmonary vascular resistance [Alsoufi et al, 2015]. The International Society of Heart and Lung Transplantation 2018 registry reported that adult congenital heart disease patients accounted for only 3% of adult heart transplants performed worldwide between 2009 and 2017 [Khush et al, 2018].

Natural history in the population, including mortality and morbidity

Survival after heart transplantation is relatively good, particularly if it is compared with the natural course of end-stage heart failure. Data from the registry of the International Society of Heart and Lung Transplantation indicated a 1-year survival of 84.5% and a 5-year survival of 72.5% [Lund et al, 2014]. This reflected a substantial improvement compared to 1-year survival (76.9%) and 5-year survival (62.7%) in the 1980s.

The development of new immunosuppressive drugs which allowed for a variety of immunosuppressive regimens, tailored to individual patients, contributed to this success, since rejection and the adverse effects of immunosuppression could be better controlled [Wilhelm, 2015]. After 20 years, approximately 21% of patients were still alive, according to the international registry [Lund et al, 2014]. In some experienced centers, long-term survival is reported to be higher [Deuse et al, 2008; Ongcharit et al, 2008; Roussel et al, 2008; Ozduran et al, 2005]. The University Hospital Zurich has published a 20-year survival rate of 55.6% [Rodriguez et al, 2014].

Five years after heart transplantation, approximately one third of patients are diagnosed with chronic allograft vasculopathy (CAV). After 10 years, CAV has been observed to occur in more than 50% of patients. Three years or more after transplantation, CAV may account for around 10% of deaths annually [Lund et al, 2014; Wilhelm, 2015].

Main existing treatment options

Commonly used immunosuppressive agents during heart transplantation are rabbit antithymocyte globulin (thymoglobulin, antithymocyte globulin-Fresenius), IL-2 receptor antagonists (basiliximab, daclizumab), muromonab-CD3, alemtuzumab, cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, everolimus, and sirolimus [Soderlund and Radegran, 2015].

Important co-morbidities

The most common co-morbidities associated with heart transplant recipients are hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, and peripheral vascular disease [Axtell et al, 2019; Kim et al, 2017; Wever-Pinzon et al, 2017]

Part II: Module SII. Non-clinical part of the safety specification

Data-lock point for this Module	31 Dec 2019
Version when Module last updated	3.0

A comprehensive, nonclinical toxicology program has been conducted to evaluate the toxicity of systemic tacrolimus. All pivotal nonclinical toxicology studies were conducted in accordance with Good Laboratory Practice and standard guidelines, including those of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.

Non-clinical safety findings of systemic tacrolimus, along with their relevance to humans, are provided in Table SII.1 below.

Table SII.1: Key Safety Findings from Non-clinical Studies

Key safety findings (from nonclinical studies)	**Relevance to human usage**
Toxicity findings include:	
Acute & repeat-dose toxicity	
The primary end organs of tacrolimus toxicity in rats and baboons were the pancreas, thymus, lymph nodes and spleen; in rats, the kidneys were also affected.	Transplant recipients receiving tacrolimus may be at higher risk for developing post-transplant diabetes mellitus, hyperglycemia and nephrotoxicity. As in patients receiving other immunosuppressants, patients receiving tacrolimus are at an increased risk of developing lymphomas. Over suppression of the immune system can increase susceptibility to infection.

Key safety findings (from nonclinical studies)	Relevance to human usage
Reproductive toxicity	
Administration of oral tacrolimus to pregnant rabbits and rats, throughout the period of organogenesis, was associated with maternal toxicity/lethality, and an increased incidence of abortion, malformation and embryofetal death at clinically relevant doses (0.5 to 6.9 times the recommended clinical dose range [0.2 to 0.075 mg/kg/day], on a mg/m^2 basis). Administration of oral tacrolimus to rats prior to mating, and throughout gestation and lactation produced maternal toxicity/lethality, marked effects on parturition, embryofetal loss, malformations, and reduced pup viability at clinically relevant doses (0.8 to 6.9 times the recommended clinical dose range, on a mg/m^2 basis). Interventricular septal defects, hydronephrosis, craniofacial malformations and skeletal effects were observed in offspring's that died.	Human data shows that tacrolimus crosses the placenta. With more data becoming available from organ transplant recipients there is no evidence of an increased risk of adverse reactions on the course and outcome of pregnancy under tacrolimus treatment, compared with other immunosuppressive medicinal products. However, cases of spontaneous abortion have been reported. There is a risk for premature delivery (<37 week), as well as for hyperkalemia in the newborn which, however, normalizes spontaneously. Human data demonstrates that tacrolimus is excreted in breast milk. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving tacrolimus.
Developmental toxicity	
Tacrolimus, given orally to pregnant rats after organogenesis and during lactation, at 1.0 and 3.2 mg/kg, 0.8 to 6.9 times the recommended clinical dose range was associated with reduced pup weights and pup viability (3.2 mg/kg only); among the high dose pups that died early, an increased incidence of kidney hydronephrosis was observed.	See above.

Key safety findings (from nonclinical studies)	**Relevance to human usage**
Genotoxicity	
No evidence of genotoxicity was observed in bacterial (Salmonella and E. coli) or mammalian (Chinese hamster lung-derived cells) in vitro assays of mutagenicity. The in vitro Chinese hamster ovary cell/hypoxanthine-guanine phosphoribusyl-transferase (CHO/HGPRT) assay of mutagenicity or in vivo clastogenicity assays performed in mice. Tacrolimus did not cause unscheduled DNA synthesis in vitro in rodent hepatocytes.	Not Applicable as no genotoxic potential was identified preclinically.
Carcinogenicity	
Carcinogenicity studies were conducted in male and female rats and mice. In the 80-week mouse oral study and in the 104-week rat oral study, no relationship of tumor incidence to tacrolimus dosage was found. The highest dose used in the mouse was 3.0 mg/kg/day (0.9 to 2.2 times the AUC at clinical doses of 0.075 to 0.2 mg/kg/day) and in the rat was 5.0 mg/kg/day (0.265 to 0.65 times the AUC at clinical doses of 0.075 to 0.2 mg/kg/day).	Patients receiving immunosuppressive therapy are at increased risk of developing malignancies.
***General safety pharmacology findings*:**	
Cardiovascular (including potential for QT interval prolongation)	
Systemic administration of tacrolimus, at doses varying from 0.1 mg/kg to 3.2 mg/kg, resulted in changes in blood pressure, femoral or carotid arterial blood flow, heart rate and electrocardiogram (ECG) that were comparable to that seen with placebo in dogs, cats and rats.	No discernable cardiovascular risk was found in studies in dogs, cats and rats. Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, have been observed in patients using tacrolimus. Tacrolimus may prolong the QT interval and may cause *Torsades de Pointes*. Caution should be exercised in patients with risk factors for QT prolongation, including patients with a personal or family history of QT prolongation, congestive heart failure, bradyarrhythmias and electrolyte abnormalities. Hypertension is a commonly observed adverse reaction.
Nervous system	

Key safety findings (from nonclinical studies)	**Relevance to human usage**
In these studies, tacrolimus had little or no discernible effect on the central nervous system. At 0.32 to 3.2 mg/kg, tacrolimus suppressed spontaneous locomotor activity in mice. Tacrolimus also had no detectable effect on the somatic or autonomic nervous systems.	No discernable neurological risk was found in studies, in mice. Patients using tacrolimus have been reported to develop neurological complications such as headaches, tremor, seizures, and PRES.
Other	
Systemically administered tacrolimus also had little or no effect on bile secretion, gastric mucosa or gastrointestinal transit rate in mice, rats, dogs and/or cats. Intravenous administration of tacrolimus (0.32 mg/kg to 3.2 mg/kg) was associated with an increase in urine volume of 30% (Study CRR920641) while oral administration of tacrolimus (32 mg/kg) increased urine volume by 38% and Na+ excretion by 40% in rats (Study CRR920607).	Diarrhea is very commonly reported in patients using tacrolimus.

AUC: Area Under the Curve; CHO/HGPRT: Chinese Hamster Ovary cell/Hypoxanthine-Guanine Phosphoribosyl-transferase; DNA: Deoxyribonucleic Acid; ECG: Electrocardiogram; PRES: Posterior Reversible Encephalopathy Syndrome.

PART II: MODULE SIII. CLINICAL TRIAL EXPOSURE

Data-lock point for this Module	31 Dec 2019
Version when Module last updated	3.1

Overall, until the data lock point, approximately 16 300 healthy volunteers and patients have been enrolled into the tacrolimus program.

The data on specific exposure to tacrolimus systemic and the data on race and/or ethnicity are not available for tacrolimus systemic in the Prograf programme, since these data were either not specifically captured or retrievable from the legacy clinical development program.

Overview of Advagraf Studies

Healthy Volunteers

Twelve biopharmaceutical studies and 2 drug interaction studies were conducted with Advagraf in a total of 298 healthy volunteers. The majority of volunteers completed the studies. Overall, 12/298 (4.0%) withdrew due to an adverse event; 10/298 (3.4%) volunteers withdrew for other reasons.

Overall Exposure in Kidney transplantation

A total of 1689 adult kidney transplant recipients received at least one dose of tacrolimus as Advagraf in the clinical development program for kidney transplantation. A total of 620 kidney transplant recipients have been exposed to Advagraf for at least 1 year, 119 kidney transplant recipients have been exposed to Advagraf for at least 5 years and 17 kidney transplant recipients have been exposed to Advagraf for at least 6 years. A summary of the enumeration of patients in the clinical development program for Advagraf in kidney transplantation is provided in Table SIII.1 and Table SIII.2.

Table SIII.1: Duration of exposure

Kidney transplant		
Years completed in the study	Persons	Person years
(All Adult Kidney transplant recipients)	1689	4777
1 year completed	620	620
2 years completed	503	1006
3 years completed	410	1230
4 years completed	306	1224
5 years completed	119	595
6 years completed	17	102

Table SIII.2: Studies

All Adult de novo kidney transplant recipients	Persons	Person years
	1519	3202
1 year completed	495	495
2 years completed	385	770
3 years completed	298	894
4 years completed	197	788
5 years completed	51	255
Study 02-0-158	214	1709
1 year completed	187	187
2 years completed	167	334
3 years completed	150	450
4 years completed	137	548
5 years completed	38	190
Conversion studies		
All Adult kidney transplant recipients converted to Advagraf†	170	1575
1 year postconversion completed	125	125
2 years postconversion completed	118	236
3 years postconversion completed	112	336
4 years postconversion completed	109	436
5 years postconversion completed	68	340
6 years postconversion completed	17	102

All patients who received at least one dose of study drug (Integrated Safety Analysis Set)

1 year completed: last dose day ≥ 335; 2 years completed: last dose day ≥ 700; 3 years completed: last dose day ≥ 1065; 4 years completed: last dose day ≥ 1430; 5 years completed: last dose day ≥ 1795; 6 years completed: last dose day ≥ 2160

† Patients participating in conversion studies and crossover trials were counted in each of the pertinent columns (e.g., a patient receiving treatment in each of the 2 arms of across over study would be counted in 2 drug columns).

(Source: Table 2.7.4 of CTD)

The comparative safety profile of Advagraf in adult de novo kidney transplant recipients is defined by 1 Phase 2 study (FG-506E-12-01), 3 Phase 3 studies (02-0-158, FG-506E-12-03 and PMR-EC-1210) and 2 phase 4 studies (PMR-EC-1211 and PMR-EC-1212).

De Novo Study FG-506E-12-01

During the primary study period for Study FG-506E-12-01, a majority of transplant recipients completed the 6-week study period (47/60 [78.3%] and 45/59 [76.3%] in the Advagraf and Prograf groups, respectively).

De Novo Study 02-0-158

During the primary study period for Study 02-0-158, a majority of transplant recipients completed the 12-month study period (183/214 [85.5%], 179/212 [84.4%] and 151/212 [71.2%] in the Advagraf, Prograf and Neoral groups, respectively).

De Novo Study FG-506E-12-03

During the primary study period for Study FG-506E-12-03, a majority of transplant recipients completed the 12-month study period (257/331 [77.6%] and 275/336 [81.8%] in the Advagraf and Prograf groups, respectively).

De Novo Study PMR-EC-1210

During the primary study period for Study PMR-EC-1210, a majority of transplant recipients completed the 6-month study period (699/903 [77.4%] and 260/311 [83.6%] in the Advagraf and Prograf groups, respectively).

De Novo Study PMR-EC-1211

A total of 936/1138 [82.2%] of transplant recipients in the safety analysis set (SAF) completed the study period of 24 weeks.

De Novo Study PMR-EC-1212

A total of 625/730 [85.6%] of transplant recipients in the intent-to-treat population (transplanted and randomized) completed the study period of 52 weeks.

Conversion Studies 02-0-131, FG-506E-12-02 and FJ-506E-KT01

During the primary study period for Study 02-0-131, all patients who received Advagraf completed the 4-week study. During the primary study period for Study FG-506E-12-02, 64/69 (92.8%) patients completed the 8-week study. During the primary study period for Study FJ-506E-KT01, 34/37 (91.9%) patients completed the 12-week study.

Overall Exposure in Liver transplantation

The comparative safety profile of Advagraf in liver transplant recipients is defined by Phase 3 Study FG-506E-11-03, phase 2 Study FG-506-11-01, and phase 3b Study PMR-EC-1106/1107.

De Novo Study FG-506-11-01

An open label multicenter comparison of the pharmacokinetics of tacrolimus in 129 adults (18 to 65 years) liver transplant recipients patients undergoing primary liver transplantation was randomized 1:1 to a Prograf Capsules or an Advagraf based immunosuppressive regimen, with 62 patients randomized to Prograf Capsules and 67 patients randomized to Advagraf (study period of 6 weeks).

De Novo Study FG-506E-11-03

During the primary study period for Study FG-506E-11-03, more than 65% of the male transplant recipients completed the 12-month study period (Advagraf: 106/162 [65.4%]; Prograf: 114/171 [66.7%]). In addition to the 12-month data from Study FG-506E-11-03, more than 4 years (median duration of dosing of 2.0 years) of posttransplant safety data are provided for the cohort of male patients who received Advagraf. Seventeen additional male patients withdrew from the study after the 12-month primary study period.

De Novo Study PMR-EC-1106/1107

A total of 615/857 (71.8%) of transplant recipients in the SAF completed the study period of 24 weeks.

Conversion Study 02-0-152 (Adults)

During the primary study period for Study 02-0-152, 38/40 (95.0%) male patients completed the 8-week study period. During the longer-term follow-up for over 5 years (median duration of dosing of 5.4 years), 14 additional male patients withdrew from the study while receiving Advagraf.

Conversion Study 03-0-160 (Pediatric)

In Study 03-0-160, a study in stable liver transplantation in pediatric patients (5 to 13 years old) converted from Prograf Capsules to Advagraf, 18/19 (94.7%) patients enrolled in the study completed the primary analysis period. All 18 patients who completed the pharmacokinetic period of the study enrolled in the clinical continuation period of the study. The patients were followed for more than 4 years (median duration of dosing of 4.4 years) and 2/18 (11.1%) discontinued the study, both due to adverse events.

Overview of Modigraf Studies

The clinical development program for tacrolimus granules included a single Phase 1 study (Study 95-0-001) to compare the bioavailability of tacrolimus immediate-release capsules (Prograf) and tacrolimus granules (Modigraf) in healthy subjects (32 subjects; 8 weeks study duration); a Phase 2 study (Study FG-506-01-08) to assess the safety, efficacy and pharmacokinetics of tacrolimus granules in children undergoing liver allograft transplantation (28 patients; 12 months study duration); and a Phase 3 study (Study FG-506-01-13) to investigate the safety and efficacy of a tacrolimus granules regimen compared to a ciclosporin-microemulsion based standard regimen in pediatric primary liver transplant recipients (91 patients; 12 months study duration).

Supportive data were provided by 6 small Japanese studies with tacrolimus granules in pediatric liver and kidney transplant recipients (58 patients; study duration ranging from 4 to 12 weeks).

No studies have been performed with Modigraf granules to investigate prophylaxis of transplant rejection in heart transplant recipients and treatment of rejection in allograft recipients. However, since tacrolimus is the active substance in both Prograf Capsules and Modigraf formulations, the mechanism of action will also be identical.

PART II: MODULE SIV. POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Data-lock point for this Module	31 Dec 2019
Version when Module last updated	3.0

Systemic tacrolimus is marketed since 02 Apr 1993. Due to the maturity of the compound marketing experience of over 26 years; the vast clinical experience accumulated over many years of using tacrolimus as an immunosuppressant in organ transplantation, compensates for the limitations of the human safety database for tacrolimus usage in populations not studied during the clinical development programme.

PART II: MODULE SV. POSTAUTHORIZATION EXPERIENCE

Data-lock point for this Module	31 Dec 2019
Version when Module last updated	3.0

SV.1 Postauthorization exposure

SV.1.1 Method used to calculate exposure

Given the uncertainty of the therapy duration, types of treatment and compliance, market experience is not calculated in number of patients, but in patient-days or patient-years. The numbers must be interpreted with care. The market experience has been calculated using data from available sales volume and assumes that on average 5 mg/day sold, accounts for 1 patient-day.

Patient-year exposure was calculated using the following formula:

Patient-year = milligrams sold (mg) / Average daily dose (5 mg) / 365.25 (days).

SV.1.2 Exposure

On 31 Dec 2019, the estimated cumulative patient exposure to tacrolimus amounts to be approximately 6.55 million patient-years.

Cumulative exposure data for the 3 formulations is presented in Table SV.1.

Table SV.1 Cumulative Exposure from Marketing Experience

Patient-years			
Prograf (Capsules)	**Advagraf (Prolonged-release capsules)**	**Modigraf (Granules)**	**Total**
5 325 828	1 208 759	17 598	6 552 185

PART II: MODULE SVI. ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Data-lock point for this Module	31 Dec 2019
Version when Module last updated	3.0

Potential for misuse for illegal purposes

There is limited or no potential for illegal use of tacrolimus. Euphoria and elevated mood have been reported with the use of tacrolimus. Experience from accidental, as well as intentional overdose has shown that tacrolimus is unsuitable for suicidal purposes. Misuse is also unlikely, due to the limited and specific indication for organ transplantation.

PART II: MODULE SVII. IDENTIFIED AND POTENTIAL RISKS

Data-lock point for this Module	31 Dec 2019
Version when Module last updated	3.2

SVII.1 Identification of safety concerns in the initial RMP submission

Section SVII.1 is not applicable, as this RMP is not an initial RMP submission.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the risk management plan

Not applicable.

SVII.1.2 Risk considered important for inclusion in the list of safety concerns in the risk management plan

Not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated risk management plan

There is one new safety concern in this updated RMP, i.e., the important identified risk 'Interaction with other medication and herbal drugs'. This well-known identified risk, covered in Summary of Product Characteristics (SmPC) Sections 4.4 and 4.5, is not a new identified risk but is considered important for inclusion in the list of safety concerns because the continued characterization of interactions is of particular importance given the narrow therapeutic index of tacrolimus and the potential for serious consequences due to underexposure or overexposure to tacrolimus.

The 2 important potential risks, are 'Exchangeability between the granule and capsule formulations of tacrolimus' (Important potential risk for Modigraf) and 'If administered accidentally either arterially or perivascularly, the reconstituted solution may cause irritation at the injection site' (Important potential risk for Prograf concentrate for solution for infusion), have been combined into the important identified risk 'Medication errors', which has been renamed as 'Medication errors resulting in under or over exposure to tacrolimus-containing medicinal products with potentially serious consequences'.

The important identified risk 'Neoplasms' has been renamed as 'Malignant neoplasms'.

Considering the guidance provided in the Good Pharmacovigilance Practices Module V Revision 2, the marketing authorization holder proposes to remove the below safety concerns from the EU-RMP as Important identified/potential risks:

- Blood cell changes
- Cardiac arrhythmias
- Coagulopathies
- Diabetogenicity
- Diarrhea
- Drug Interaction with mycophenolate mofetil

- Electrolyte changes
- Galactose intolerance
- Gastrointestinal (GI) perforation
- Hepatic and renal dysfunction
- Hypertension
- Neurological and visual disorders
- Prolonged QT interval
- Pure red cell aplasia (PRCA)
- Torsade de Pointes (TdP)

For these risks, no further evaluation (other than routine pharmacovigilance) as a part of the pharmacovigilance plan is necessary. For risk minimization, routine risk minimization measures are assessed as being sufficient, i.e., communication in the SmPC and package leaflet.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- **Pure red cell aplasia** – PRCA is characterized by the inhibition of bone marrow erythropoiesis. There are multiple factors involved in its development, such as viral infections (parvovirus B19, Epstein Barr virus), or secondary to other disorders (such as systemic lupus erythematosus or lymphoproliferative disorders) or it could be due to the immunosuppressive effect of tacrolimus and other concomitantly used immunosuppressants (leading to susceptibility to viral infections that are well known to be a cause of bone marrow suppression). PRCA is listed as an adverse drug reaction (an ADR) in the SmPC Section 4.8, Undesirable effects (frequency: unknown) and Section 4.4 of the SmPC (Special warnings and precautions for use) includes a warning that cases of PRCA have been reported in patients treated with tacrolimus. The Astellas global safety database contains a relatively small number of reported events of the preferred term (PT), Aplasia pure red cell, for which tacrolimus is reported as suspect drug or concomitant medication (n = 127 cumulatively up to 31 Dec 2019, including invalid cases), considering the product's time in the market and an estimated cumulative exposure from marketing experience of approximately 6.55 million patient-years.
- **Torsade de Pointes and Prolonged QT interval** - The exact incidence of drug-induced TdP in the general population is unknown and is considered very rare. Drug-induced TdP typically arises with the use of medications that cause QT prolongation beyond 500 ms, inducing polymorphic ventricular tachycardia [Abdelmawla and Mitchell, 2006; Roden, 2004; Yap and Camm, 2003]. Patients with already reduced repolarization reserve (such as those with heart failure), who may not tolerate the insult or even a small increase in the QT interval, may be at an increased risk for TdP when exposed to QT prolonging drugs. The majority of the patients, in whom TdP develops in association with the use of non-cardiac drugs, have at least 1 or 2 risk factors, i.e., 96% and 72%, respectively [Zeltser et al, 2003]. Tacrolimus may prolong the QT interval and may cause TdP.

Consequently, the SmPC contains a warning for patients having Congenital long QT syndrome or acquired QT prolongation, risk factors for QT prolongation, or using concomitant medications known to prolong the QT interval induced electrolyte abnormalities or known to increase tacrolimus exposure. TdP and electrocardiogram (ECG) QT prolonged are listed as ADRs in the SmPC Section 4.8 (frequency: very rare). The Astellas global safety database contains a relatively small number of reported events for the standardized MedDRA query Torsade de pointes/QT prolongation [narrow], and the PTs Torsade de pointes, ECG QT prolonged or Long QT syndrome for which tacrolimus is reported as suspect drug or concomitant medication (107, 9, 48 and 4 events cumulatively up to 31 Dec 2019, respectively, including invalid cases), considering the product's time in the market and an estimated cumulative exposure from marketing experience of approximately 6.55 million patient-years.

Known risks that require no further characterization and are followed up via routine pharmacovigilance and for which the risk minimization measures in the product information are part of standard clinical practice (embedded in clinical guidelines for the management of SOT recipients)

There are many guidelines for the care of SOT recipients, often specific to the transplanted organ or the type of complication and by the region. Kidney and liver transplantation represent 88% of all SOT procedures (65% and 23%, respectively) [GODT, 2017]. The Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group, formed in 2015, composed of 20 leading kidney and liver transplant specialists, from 9 countries across the EU, published widely used recommendations for the long-term management of modifiable risks in kidney and liver transplant patients in 2017 [Neuberger et al, 2017]. Additionally, the COMMIT Group included a checklist, offering a systematic and efficient way to implement screening and monitoring of modifiable risks in the clinical setting. The recommendations were intended to complement local guidelines. The recommendations address the following identified modifiable risk factors: nonadherence, intra-patient variability in immunosuppressive exposure, underimmunosuppression, adverse effects related to immunosuppression, Donor specific antibodies, early ischaemic injury and delayed graft function (kidney)/ early allograft dysfunction and nonanastomotic biliary strictures (liver), cardiovascular and metabolic complications. The majority of the below identified risks are discussed within the recommendations of COMMIT.

- **Blood cell changes** – This risk comprises Anaemia, Leukocytosis, Leukopenia, Neutropenia, Thrombocytopenia, and Pancytopenia, which are included as ADRs in the SmPC Section 4.8 based on post-marketing experience with tacrolimus. These hematological changes are observed in transplant patients, during tacrolimus treatment, and are collectively placed under the umbrella risk of "blood cell changes" at the time of the first RMP.

  The development of anemia and single or multi-lineage cytopenias has been extensively characterized in the post-transplant setting, and the monitoring of blood cells is a standard clinical practice for any patient under immunosuppression.

- **Anemia** - Post-transplant anemia commonly occurs and may be due to surgery, medication side-effects, infection, or organ rejection. Anemia due to inappropriately low levels of erythropoietin or iron deficiency is common. Anemia is a recognized determinant of intra-patient variability of tacrolimus levels and is discussed as such in the COMMIT monitoring guidance. Special attention for anemia is warranted in patients with malnourishment and iron deficiency, which are frequent conditions among the transplant populations. Anemia is also a known risk factor for the development of cardiovascular events and is part of hematological monitoring in post-transplant patients [Yang et al, 2015].
- **Leukocytosis** - Cases of leukocytosis are commonly observed in the post-transplant period and have various etiologies including post-surgical stress, infections, transplant rejection, resolution of pre-transplant hypersplenism, and medication side-effects [Venegas et al, 2006; Singh et al, 1998]. Leukocyte count is part of standard monitoring after any type of transplant.
- **Leukopenia, Neutropenia, Thrombocytopenia, Pancytopenia -** Various post-transplant cytopenias have been characterized, including pancytopenia. The spectrum of hematologic disorders after SOT includes single or multilineage cytopenias of infectious, inflammatory, immune-mediated, or drug-related etiology; post-kidney-transplant erythrocytosis; thrombotic microangiopathy; infection-induced hemophagocytic syndrome; graft-versus-host disease; post-transplant lymphoproliferative disorder; venous thromboembolism; and coagulopathy [Smith, 2010].

Monitoring of hematological complications is standard practice and is included in Section 4.4 of the SmPC and discussed within the recommendations of COMMIT [Neuberger et al, 2017] and/or other clinical guidelines for the management of SOT recipients.

- **Cardiac arrhythmias** - Supraventricular arrhythmias and Ventricular arrhythmias are included as ADRs in the SmPC Section 4.8, based on the post-marketing experience with tacrolimus. Cardiac arrhythmias are common in orthotopic heart transplant recipients, particularly in the early postoperative period [Simonenko, 2019]. Premature atrial complexes and premature ventricular complexes are especially frequent, with a reported incidence of over 60 % [Eisen and Kusmirek, 2015]. The main underlying mechanisms of arrhythmias, in a transplanted heart, are due to surgery (denervation), rejection or cardiac allograft vasculopathy, the recipient's prior drug exposure or from the transplanted heart itself (coronary artery disease). Supraventricular and ventricular tachycardias are prevalent among kidney transplant patients (30%, with coronary atherosclerosis and male sex as predominant factors) [Marcassi et al, 2011]. Cardiovascular mortality in kidney transplant recipients is shown to be substantially elevated particularly in the first year of transplantation and the complex ventricular arrhythmia has been pointed as one of the etiologies of sudden death. Atrial arrhythmias are common post-lung transplant, with an incidence reported between 15% to 46% [Dutton et al, 2019]. The most frequently occurring atrial arrhythmia post-lung transplant

is atrial fibrillation. Ventricular arrhythmias were less prevalent. Current evidence suggests causation is, likely, multifactorial. Causative factors include old age, male sex, dilated right atrium, and chronic obstructive pulmonary disease.

Cardiac monitoring by ECG in the post-operative period is standard clinical practice; an annual cardiovascular check-up is recommended within the COMMIT guidelines [Neuberger et al, 2017].

- **Coagulopathies** - The liver plays a central role in the maintenance of hemostasis at the site of synthesis, for a vast majority of proteins required for the regulation of coagulation and fibrinolysis. Thus, tacrolimus should be used with caution in the impairment of liver cell function since it can disturb hemostasis. Coagulopathies and thrombotic microangiopathy are included as adverse reactions in Section 4.8 of the SmPC. Additionally, monitoring of hematology parameters and coagulation values has also been included in Section 4.4 of the SmPC.

  Etiology of coagulopathies has been fully characterized in liver transplant patients and, to a lesser extent, in other SOT settings. Pre-transplant patients may present with a hypercoagulable state, which persists in the early transplant period. The use of anti-platelet or anti-coagulant therapy warrants frequent monitoring. Blood work for coagulation status is performed more frequently in the early post-transplant period. Guidelines place emphasis on coagulation management in regard to monitoring and treatment protocols before, during and after the surgery, predominantly with regard to hemostatic balance in liver transplantation [EASL, 2016]. End-stage liver disease causes disruption of the hemostatic system due to the hepatic protein synthetic dysfunction [Northup and Reutemann, 2018]. Monitoring of coagulation status is a standard practice in the post-transplant setting and is included in the clinical guidelines for the management of SOT recipients [Kasiske et al, 2010].

- **Diabetogenicity** - New-onset diabetes and impaired glucose tolerance are amongst the most serious metabolic complications of SOT. New onset diabetes mellitus after transplantation has been reported to occur in 4% to 25% of renal transplant recipients, 2.5% to 25% of liver transplant recipients, 4% to 40% of heart transplant recipients, and 30% to 35% of lung transplant recipients [Pham et al, 2011]. Lacking consensus regarding the definition of new onset diabetes after transplantation, differences in duration of follow-up and the presence of risk factors may have led to large variations in the reported incidences [Pham et al, 2011]. Over immunosuppression increases the probability of developing metabolic complications such as diabetes mellitus. Hyperglycemic conditions and diabetes mellitus are listed as ADRs in the SmPC Section 4.8. Additionally, Section 4.4 of the SmPC includes a warning that, fasting blood glucose levels should be monitored on a routine basis during the initial post-transplant period. Clinical practice guidelines, such as the COMMIT guidelines [Neuberger et al, 2017], include recommendations for the management and prevention of metabolic disorders such as diabetes.

- **Diarrhea** - Causes of post-transplant Diarrhea include infectious causes (bacterial or viral) and non-infectious causes such as exposure to immunosuppressants or other medications (e.g., laxatives, antibiotics, antidiabetics) or comorbidities such as post-transplant lymphoproliferative disorder or colon cancer. Diarrhea is a well-known adverse reaction of tacrolimus in post-transplant patients, with a frequency listed in the SmPC Section 4.8 as 'very common'. Because levels of tacrolimus in the blood may significantly change during the Diarrhea episodes, extra monitoring of tacrolimus concentrations is recommended during the episodes of Diarrhea. Additionally, the SmPC includes a warning in Section 4.4 to sufficiently manage this risk. Clinical practice guidelines, such as the COMMIT guidelines [Neuberger et al, 2017], include Diarrhea among the determinants of tacrolimus variability. More frequent assessment of tacrolimus trough concentrations and refined dose adjustments are recommended.
- **Electrolyte changes** - Electrolyte abnormalities (including hyponatraemia, hypomagnesaemia, hyperkalemia, hypokalaemia, hypocalcaemia, hypophosphataemia and hyperphosphataemia) are listed as ADRs in the SmPC Section 4.8. Additionally, Section 4.4 of the SmPC includes a warning that electrolytes (particularly potassium) should be monitored on a routine basis during the initial post-transplant period. Furthermore, caution should also be exercised in patients using concomitant medications which can induce electrolyte abnormalities. Clinical practice guidelines include recommendations for the management of electrolyte changes. For example, the Kidney Disease Improving Global Outcomes guidelines recommend to measure, after kidney transplantation, serum calcium and phosphate levels, at least, weekly until stabilization [Kasiske et al, 2010]. International guidelines for the care of heart transplant recipients include recommendations for regular screening for adverse events of calcineurin inhibitors, such as hypophosphataemia, hypomagnesaemia and hyperkalemia [Costanzo et al, 2010].
- **Hepatic and renal dysfunction** - It has been reported that up to 25% of patients will have some degree of abnormal liver functions during the immediate post-transplant period. Many factors have been implicated in the causation of post-transplantation liver disease, including infection, preexisting liver disease, and drug toxicities [Ahsan and Venkateswara, 2002].

  Acute kidney injury is a frequent complication of nonrenal SOT with a reported incidence ranging from 16.9% to 56% and dialysis dependency ranging from 4.6% to 8% [Rossi and Vella, 2016]. Impairment of renal function is one of the most common complications following an orthotopic liver transplant. In one large analysis of more than 69 000 non-renal transplant recipients (data from the Scientific Registry of Transplant Recipients), the cumulative incidence of renal dysfunction (defined as a glomerular filtration rate of <30 mL/min/1.73m2) in those who had undergone orthotopic liver transplant) was 8.0%, 13.9% and 18.1% after 1 year, 3 years and 5 years of transplantation, respectively [Ojo et al, 2003]. Abnormality of the liver function, insufficient functioning of the kidneys, reduced production of urine and impaired or painful urination are among the side effects of tacrolimus. Hepatic failure and renal impairment/failure are listed as ADRs in the

SmPC. Additionally, Section 4.4 of the SmPC includes a warning that liver and renal function tests should be monitored on a routine basis during the initial post-transplant period.

The monitoring of renal and hepatic function is standard practice and is discussed within the recommendations of COMMIT [Neuberger et al, 2017] and/or other clinical guidelines for the management of SOT recipients.

- **Hypertension** – Hypertension is one of the most frequent complications of SOT; about 70–90% of this population has high blood pressure or require antihypertensive therapy. Although the etiology of hypertension after SOT is multifactorial, immunosuppressive medications, such as calcineurin inhibitors and corticosteroids, are known to have hypertensive effects [Zbroch et al, 2012]. Hypertension is listed as ADR in the SmPC Section 4.8. Additionally, Section 4.4 of the SmPC includes a warning, that the blood pressure should be monitored on a routine basis during the initial post-transplant period. Recommendations for the management of hypertension are included in clinical practice guidelines for the care of transplant recipients. For example, annual screening for hypertension is recommended within the COMMIT guidelines [Neuberger et al, 2017].
- **Neurological and visual disorders** - After organ transplantation, patients may suffer from relatively mild neurological symptoms, such as tremors, to severe complications including disturbance of consciousness, seizures and encephalopathy. While the spectrum of neurological complications varies with the type of organ transplanted, the indication for the procedure, and the intensity of long-term required immunosuppression, major neurological complications occur with all SOT types. Few neurologic complications occur exclusively in a specific transplant population, but both in the early days and throughout their post-transplantation course, recipients of different tissues and organs have predictably varied complication patterns [Pruitt et al, 2013]. Patients may have involvement of the central or peripheral nervous system [Pedroso et al, 2017]. It is estimated that approximately one-third of SOT patients will experience a neurological complication [Senzolo et al, 2009]. Liver transplant recipients appear to be at greater risk for developing neurological symptoms in comparison with other types of SOT [Weis and Thabut, 2019]. A wide range of nervous system disorders have been described during the use of tacrolimus, including more general symptoms such as dizziness, convulsions, depressed level of consciousness, and paresthesia, to specific syndromes such as peripheral neuropathies, posterior reversible encephalopathy syndrome and John Cunningham (JC) virus associated progressive multifocal leukoencephalopathy. These events are listed as ADRs in the SmPC. Section 4.4 of the SmPC includes a warning that the neurological status should be monitored on a routine basis during the initial post-transplant period. Additionally, Section 4.4 of the SmPC carries a warning about neurotoxicity which states that in case of the development of suspect symptoms of encephalopathies, immediate confirmatory medical imaging and other suitable measures including tacrolimus discontinuation should be considered.

It has long been recognized that ocular complications occur in SOT patients. A large percentage of these are due to opportunistic infections [Ng et al, 1998]. A study in heart transplant patients showed that older patients and those with a longer survival time after transplantation are more likely to have ophthalmic complications [Quinlan and Salmon, 1993]. The most frequent ophthalmological diagnoses in patients after a kidney transplant include cataracts, diabetic retinopathy and hypertensive angiopathy. Visual acuity deterioration was seen in 60% of patients after kidney transplant [Raczyńska et al, 2018]. Visual disorders including blurred vision, increased sensitivity to light, and cases of optic neuropathy and (transient) blindness are reported side-effects of tacrolimus. These events are listed as ADRs in the SmPC. Section 4.4 of the SmPC includes a warning about eye disorders, sometimes progressing to loss of vision. Additionally, Section 4.4 of the SmPC carries a warning that visual status should be monitored on a routine basis during the initial post-transplant period and includes the recommendation to report changes in visual acuity, changes in color vision, blurred vision, or visual field defect.

Monitoring of neurological status and visual complications are standard practice and are included in Section 4.4 of the SmPC and discussed within the recommendations of COMMIT [Neuberger et al, 2017] and/or other clinical guidelines for the management of SOT recipients.

Known risks that do not impact the benefit risk profile

- **Galactose intolerance** - Galactosemia, is a rare autosomal recessive disorder of galactose metabolism, caused by a deficiency of the enzyme galactose-1 phosphate uridyltransferase. The incidence varies across nations; the worldwide incidence of galactosemia is about 1 per 70,000 [Schweitzer, 1995].

  Tacrolimus capsules contain lactose and hence for patients with this hereditary disorder, cautions are included in Section 4.4 of the SmPC. The Astellas global safety database contains no cases for tacrolimus reporting galactose intolerance (PT Galactosaemia or PT Galactose intolerance). In the literature, no publications were identified describing an association between tacrolimus and galactose intolerance. In accordance with the Rapporteur assessment comment in the Periodic safety update report (PSUR) assessment report (PSUR covering the period of 01 Apr 2015 to 31 Mar 2018; Procedure number EMEA/H/C/PSUSA/00002839/201803), galactose intolerance has been retired as targeted medical event and the risk is removed from the RMP.

Other reasons for considering the risks not important

- **GI perforation** - GI has been reported in patients treated with tacrolimus. The GI perforation in transplanted patients is a multifactorial phenomenon. GI perforation in transplant patients consists of two phases, early and late after transplantation surgery. In the early phase, intestinal perforation is considered a complication of transplantation surgery, although the effect of tacrolimus may not be completely excluded. In the late phase, the main causes of GI perforation that may be associated with immunosuppression are e.g., GI infection or malignant neoplasm. Risk group includes

those with pre-existing GI conditions diverticulitis, pre-existing infection or prolonged use of corticosteroid therapy [de'Angelis et al, 2016; Lucan and Berardinelli, 2016; Helderman and Goral, 2002]. The GI perforation is listed as ADR in the SmPC Section 4.8. Because of the seriousness of the event and the requirement for prompt treatment to prevent the development of a life-threatening situation, it is also included as a warning in Section 4.4 of the SmPC.

- **Drug Interaction with Mycophenolate Mofetil:** From the evaluations performed so far, there is no evidence to support a pharmacokinetic drug-drug interaction between mycophenolic acid and tacrolimus. Changes in tacrolimus levels occur as a function of changes in clearance due to pathophysiological reasons. For example, it has been shown that a decrease in plasma albumin, plasma protein and hematocrit leads to an increase in clearance and consequently, a decrease in tacrolimus exposure. Whereas the increase in albumin and hematocrit leads to decreased clearance and increased tacrolimus levels [Undre, 2003]. The important identified risk 'Interaction with other medication and herbal drugs' covers all drug-drug interactions. Therefore, if new information emerges about changes in tacrolimus levels when co-administered with Mycophenolate Mofetil (MMF), this would be part of the important identified risk 'Interaction with other medication and herbal drugs'.

For all the risks which have been proposed to be removed from the list of safety concerns in this RMP, the marketing authorization holder would like to emphasize that it will continue to monitor these risks through routine pharmacovigilance activities, including signal management activities.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified Risk:	**Malignant neoplasms**
MedDRA term(s)	Standardized MedDRA Query (SMQ) Malignant or unspecified tumours
Potential mechanisms:	Posttransplant malignancies are thought to develop by 3 mechanisms [Acuna, 2018; Katabathina et al, 2016], i.e., - De novo development. The proposed pathogenic mechanisms include impaired immunosurveillance of neoplastic cells, weakened immune activity against oncogenic viruses, chronic stimulation of the immune system, direct carcinogenic effects of immunosuppressive agents, pre-existing cancer risk factors, factors related to end-stage organ disease or dialysis in the case of kidney transplant recipients. - Donor-related transmission - Recurrence of a recipient's pre-transplant malignancy
Evidence source(s) and strength of evidence:	The increased risk in transplant recipients for developing cancer has been well described in the literature and Clinical Practice Guidelines and is also based on data from tacrolimus post-marketing experience.

Important Identified Risk:	**Malignant neoplasms**
Characterization of the risk:	SOT recipients have an increased risk of cancer compared with the general population. The incidence varies by organ transplanted and by different types of malignancies. The mechanisms that lead to the observed excess risk in transplant recipients have not been fully elucidated but are likely multifactorial. A meta-analysis, published in 2018, assessed all possible correlations between renal transplantation and the risk of cancer at different sites [Wang et al, 2018]. The meta-analysis included 11 prospective cohort studies, reporting data on 79 988 renal transplant recipients. The findings suggest that patients who receive renal transplantation have an increased risk of cancer at most sites, apart from uterine and prostate cancer patients. In liver transplant recipients, the most common malignancies were lymphomas and skin cancers (including squamous cell carcinoma and Kaposi's sarcoma), followed by Gastrointestinal (GI), Genitourinary, Lung, Oropharyngeal [Sint et al, 2010; Fung et al, 2001]. A meta-analysis on the prevalence of post-transplant malignancies in heart transplant recipients, including 55 studies comprising 60684 heart transplant recipients, indicated that the most frequent cancers were GI (7.6%), skin (5.7%) and hematologic/blood (2.5%) [Lateef et al, 2020].
Risk factors and risk groups:	Risk factors for posttransplant malignancy include traditional risk factors such as advancing age, smoking, drinking alcohol, obesity, sun exposure, and family history, and risk factors that are unique to the transplant population, including immunosuppression, oncogenic viral infections, and disease-specific associations (e.g., factors related to end-stage organ disease or dialysis in the case of kidney transplant recipients) [Rossi and Klein, 2019; Acuna, 2018].

Important Identified Risk:	**Malignant neoplasms**
Preventability:	Section 4.4 of the SmPC includes a warning for Epstein-Barr virus (EBV)-associated lymphoproliferative disorders, especially for very young EBV seronegative children where careful monitoring of EBV serology is recommended after starting tacrolimus. Furthermore, SmPC Section 4.4 includes a warning for malignant skin changes with a recommendation that exposure to sunlight and UV light should be limited by wearing protective clothing and that a sunscreen with a high protection factor should be used. In several guidelines is described how to screen and monitor transplant patients in order to prevent and/or manage malignant neoplasms. Acuna et al [2017] identified 13 Clinical Practice Guidelines for posttransplant care that include recommendations for cancer screening. Weaknesses in the available recommendations are: • There is a lack of direct evidence to support cancer screening recommendations. Although screening for skin cancer is addressed in almost all CPGs reviewed, the inclusion of screening recommendations for other malignancies was variable. • Most of the recommendations for cancer screening are targeted towards kidney recipients, and fewer recommendations exist for other SOT recipients. • Relevant stakeholders such as oncology specialists, primary care providers and public health experts were not involved in the formulation of the screening recommendations.
Impact on the risk-benefit balance of the product:	Development of malignant neoplasms, which are life-threatening conditions, are an important identified risk and have an impact on the risk-benefit balance. Routine risk minimization measures are put in place to mitigate this risk.
Public health impact:	Malignancy is among the leading causes of death among SOT recipients. Susceptibility depends on complex interactions between e.g., pharmacological immunosuppression, smoking, alcohol consumption, viral infection, and genetic predisposition.

CPG: Clinical Practice Guidelines; EBV: Epstein-Barr virus; GI: Gastrointestinal; MedDRA: Medical Dictionary for Regulatory Activities; SmPC: Summary of Product Characteristics; SMQ: Standardized MedDRA query; SOT: Solid Organ Transplant; UV: Ultraviolet

Important Identified Risk:	**Serious infections and reactivation of pre-existing infections**
MedDRA term(s)	SOC Infections and Infestations
Potential mechanisms:	Immunosuppressive agents inhibit the immune system resulting in an increased risk of infections. Infections occur more commonly during the first year of transplant, when immunosuppression levels are highest.
Evidence source(s) and strength of evidence:	This important identified risk has been well described in the literature and Clinical Practice Guidelines and is also based on data from tacrolimus post-marketing experience.
Characterization of the risk:	Patients receiving immunosuppressants, including tacrolimus, are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including infection reactivation (for e.g., Hepatitis B reactivation) and opportunistic infections (for e.g., a human polyomavirus, JC virus, associated progressive multifocal leukoencephalopathy). These infections may lead to serious, including fatal, outcomes (SmPC Section 4.4). Severe infections may occur during 3 classical periods, i.e., the post-surgical phase (< 4 weeks after transplantation), the period of maximum immunosuppression (1 to 12 months after transplantation) and thereafter (> 12 months after transplantation). During the first month after transplantation, infections result from surgical complications, donor-derived infections, pre-existing recipient infections and nosocomial infections. Infections occurring in the period of 1 to 12 months after transplantation are mainly due to reactivation of latent infections such as cytomegalovirus, herpes simplex virus, varicella-zoster virus and opportunistic pathogens. Infections occurring after 12 months include community-acquired and healthcare-associated infections [Timsit et al, 2019].

Important Identified Risk:	**Serious infections and reactivation of pre-existing infections**
Risk factors and risk groups:	Increased risk and severity of infection in kidney transplant recipients are explained by many factors, including the condition of the recipient, such as surgical complications, or the use of indwelling catheters; the possibility of transmission of infection from donor to recipient; overimmunosuppression; active smoking; and obesity, etc. Viral infections in kidney transplant recipients, which occur more frequently during the first few months, are most likely in the context of greater immunosuppression. Furthermore, recipient age is often a significant risk factor for bacterial infections, but not viral/fungal infections. Type of immunosuppressive agent such as the use of induction therapy with antithymocyte globulin is also associated with viral infection. The relationship between bacterial infection in kidney transplant recipients and overimmunosuppression is well established. However, in many cases, there are additional identifiable risk factors for bacterial infection, including surgical complications, intravenous or urinary catheters, urinary retention, or vesicoureteral reflux. Patients with a tuberculin purified protein derivative-positive skin test or a positive IFN-γ release assay for tuberculosis before transplantation are also at increased risk of *Mycobacterium tuberculosis* infection after transplantation [Neuberger, 2017].
Preventability:	A warning is included in the product label (SmPC Section 4.4) on the occurrence of infections in patients receiving immunosuppressants. Recommendations for the management and prevention of infections are included in clinical practice guidelines for the care of transplant recipients.
Impact on the risk-benefit balance of the product:	Patients that use tacrolimus are at increased risk of developing infections or reactivation of pre-existing infections. These may lead to serious, including fatal, outcomes. Reducing immunosuppression to reduce the risk of infections can lead to an increased risk of graft rejection. The important identified risk of serious infections and reactivation of pre-existing infections have an impact on the risk-benefit balance.
Public health impact:	The occurrence of infections in posttransplant patients may pose a safety concern and may present a burden for national healthcare systems (e.g., due to the high rate of hospital admissions and potentially fatal outcomes).

IFN-γ: Interferon-gamma JC: John Cunningham; MedDRA: Medical Dictionary for Regulatory Activities; SmPC: Summary of product characteristics; SOT: Solid Organ Transplant

Important Identified Risk:	**Medication errors resulting in under or over exposure to tacrolimus-containing medicinal products with potentially serious consequences**
MedDRA term(s)	SMQ Medication errors [broad and narrow scope]
Potential mechanisms:	Errors in medication practice can occur at the time of prescribing, dispensing, storing, preparation and administration of tacrolimus, and the errors could be made by prescribers, pharmacists, nurses or other health care professionals involved, or even by the patients and their caregivers.
Evidence source(s) and strength of evidence:	This important identified risk is based on data from tacrolimus post-marketing experience.
Characterization of the risk:	The most frequently reported types of medication errors (up to 31 Dec 2019; applying the SMQ Medication errors [narrow scope]) are Administration errors (74%), followed by Dispensing errors (10%), Storage errors (9%) and Prescribing errors (6%). Among the administration errors, the most commonly reported PT is Product dose omission (23%), followed by the PTs Medication error (12%), Wrong technique in product usage process (12%), Incorrect route of product administration (10%) and Inappropriate schedule of product administration (10%). The majority of the cases missed information on the onset date of the medication error and/or the AE. Consequently, it is often not possible to determine if the medication error could have played a role in the development of the AEs. Prograf - Advagraf medication switch errors: Astellas markets four different formulations of systemic tacrolimus; Prograf solution for infusion, Prograf immediate release capsules, Advagraf prolonged-release capsules and Modigraf granules for oral suspension. Inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. This has led to serious adverse reactions, including graft rejection, or other adverse reactions which could be a consequence of either under- or over-exposure to tacrolimus. Communication of Prograf/Advagraf medication errors to healthcare professionals (HCPs) across the EEA was performed via a Direct Healthcare Professional Communication (DHPC) letter in 2008. This was to notify the HCPs of the issue of medication error with systemic tacrolimus.
Risk factors and risk groups:	A systematic review was published in 2018; this review investigated the epidemiology of medication errors and error-related adverse events in adults, in primary care, ambulatory care and patients' homes. Risk factors for medication errors listed in this 2018 review, related to patients, healthcare professionals and/or medications are listed below [Assiri et al, 2018].

Important Identified Risk:	**Medication errors resulting in under or over exposure to tacrolimus-containing medicinal products with potentially serious consequences**
	Patient related risk factors: polypharmacy, increased age, number of diseases or comorbidities, being female, low level of education, hospital admission and middle family income. Healthcare professional-related risk factors: more than one physician involved in their care, family medicine/GP specialty, age ≥51 years, male GP, frequent changes in prescription, not considering the prescription of other physicians, inconsistency in the information and outpatient clinic visits. Medication related risk factors: multiple medication storage locations used, expired medication present, discontinued medication repeats retained, hoarding of medications, therapeutic duplication, no medication administration routine, poor adherence and patients confused by generic and trade names.
Preventability:	Since the implementation of the risk minimization measures, in 2008, there has been a downward trend in the reporting of Advagraf – Prograf medication errors (i.e., from 72 cases in the PSUR reporting interval 01 Apr 2008- 31 Mar 2009 to 25 cases in the PSUR reporting interval 01 Apr 2018 – 31 Mar 2019).
Impact on the risk-benefit balance of the product:	Medication errors resulting in under or over exposure to tacrolimus-containing medicinal products with potentially serious consequences are an important identified risk. Immunosuppression is essential for the success of transplantation and tacrolimus has an established role in the immunosuppression protocols, emphasized in different regional and national guidelines [Lucey et al, 2013; Chadban et al, 2012; Heemann et al, 2011; Bia et al, 2010; Knoll et al, 2010; Sokal et al, 2002]. Given the narrow therapeutic index of tacrolimus and the risk of under or over immunosuppression due to medication errors, which may result in graft rejection or increased incidence of adverse reactions, medication errors could have an impact on the risk-benefit balance.
Public health impact:	Errors associated with the use of medicinal products are a major public-health burden. A post hoc analysis was performed of a prospective, randomized trial in 200 adult kidney transplant recipients to determine the incidence severity, the risk factors, and the clinical outcomes associated with medication errors and the ADRs in renal transplant recipients, receiving immunosuppression [Taber et al, 2014]. The mean study follow-up was 2.5±0.7 years. Medication errors occurred in 64% of the cohort with 12% experiencing a clinically significant medication error. Significant medication

Important Identified Risk:	Medication errors resulting in under or over exposure to tacrolimus-containing medicinal products with potentially serious consequences
	errors were associated with an increased risk of deleterious clinical outcomes, including subsequent hospital days, costs, and graft loss.

AEs: Adverse Events; ADRs: Adverse Drug Reactions; DHPC: Direct Healthcare Professional Communication; EEA: European Economic Area; GP: General Practitioner; HCP: Healthcare Professionals; MedDRA: Medical Dictionary for Regulatory Activities; PSUR: Periodic Safety Update Report; PT: Preferred term; SMQ: Standardized MedDRA query; SOT: Solid Organ Transplant

Important Identified Risk:	Interaction with other medication and herbal drugs
MedDRA term(s)	High Level Term Interactions
Potential mechanisms:	Tacrolimus is extensively metabolized via the hepatic microsomal cytochrome P- 450 3A4 isoenzyme (CYP3A4). Concomitant use of drugs or herbal remedies known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease the blood level of tacrolimus which may impact its efficacy or toxicity. Tacrolimus also shows a broad and powerful inhibitory effect on CYP3A4-dependent metabolism, thus, concomitant use of tacrolimus with drugs known to be metabolized by CYP3A4-dependent pathways may affect the metabolism of such drugs.
Evidence source(s) and strength of evidence:	This important identified risk has been well described in drug interaction studies, literature and is also based on data from tacrolimus post-marketing experience.
Characterization of the risk:	Two formal interaction studies have been performed with Advagraf (Studies F506-CL-0844 and F506-CL-0846). Since tacrolimus is the active substance in both Advagraf and Prograf Capsules, the potential for interactions is considered to be similar, which was confirmed in the two interaction studies performed as briefly summarized below. F506-CL-0844 (28 healthy adult male subjects): the AUC0-tz and AUC0-∞ for Advagraf were 6.3 and 7.5-fold higher in combination with ketoconazole (a CYP3A4 inhibitor) compared to when administered alone. Corresponding values for Prograf Capsules were 7.1 and 8.2-fold higher. C_{max} of tacrolimus increased by 4.6 and 3.5-fold for Advagraf and Prograf Capsules during co-administration with ketoconazole. The C_{max} for Advagraf was 30% lower than for Prograf Capsules when administered alone and 8% lower when co-administered with ketoconazole. For both formulations, co-administration with ketoconazole increased the time to reach maximum concentrations; for Advagraf median t_{max} increased from 2 to 4 hours post-dose whereas for Prograf Capsules median t_{max} increased from 1.0 to 3.5 hours post-dose. F506-CL-0846 (28 healthy adult male subjects): the AUC0-

Important Identified Risk:	Interaction with other medication and herbal drugs
	tz and AUC0-∞ for Advagraf were both approximately 56% lower in combination with rifampicin (a CYP3A4 inducer) compared to when administered alone. Corresponding values for Prograf Capsules were both approximately 61% lower. C_{max} of tacrolimus decreased by 47% and 24% for Advagraf and Prograf Capsules during co-administration with rifampicin. The C_{max} for Advagraf was 22% lower than for Prograf Capsules when administered alone and 45% lower when co-administered with rifampicin. The time to reach maximum concentrations of tacrolimus was similar for both formulations when administered alone and co-administered with rifampicin, with median t_{max} between 1 and 2 hours post-dose. In addition to the above-mentioned formal interaction studies, the potential interactions between tacrolimus and CYP3A4 inhibitors or inducers have been identified and characterized in literature and/or through post-marketing data surveillance. Tacrolimus in addition has also been described in literature as an inhibitor of CYP3A4 and may affect the metabolism of other medicinal products. The known pharmacokinetic drug interactions with tacrolimus are well documented in the tacrolimus SmPC and are usually reversible with prompt dose adjustment of tacrolimus or the co-administered drug(s). Other well documented interactions in the tacrolimus SmPC are e.g., non-metabolic interactions, such as potential synergistic nephrotoxicity or neurotoxicity when co-administered with medicinal products known to have nephrotoxic or neurotoxic effects, possible interactions with other medicinal products known to have high affinity for plasma proteins, or response to vaccination. Changes in mycophenolic acid exposure may occur when patients are switching from ciclosporin and mycophenolic acid co-administration to tacrolimus and mycophenolic acid or vice versa. Mechanistically ciclosporin interferes with enterohepatic recirculation of mycophenolic acid, while tacrolimus is devoid of this effect. Therapeutic drug monitoring of mycophenolic acid may be appropriate when switching from ciclosporin to tacrolimus or vice versa. Tacrolimus is a known CYP3A4 inhibitor and therefore could have an effect on the metabolism of other medicinal products.
Risk factors and risk groups:	Particularly patients that use tacrolimus and require medications or herbal remedies which are strong CYP3A4 inhibitors (e.g., such as telaprevir, boceprevir, ritonavir, ketoconazole, voriconazole, itraconazole, telithromycin or

Important Identified Risk:	Interaction with other medication and herbal drugs
	clarithromycin) or inducers (e.g., such as rifampicin, rifabutin) are at risk. Genetic CYP3A polymorphisms may have an impact on drug metabolism and a person's ability to metabolize certain drugs can be increased ("fast" metabolizers) or decreased ("poor" metabolizers). To date, the influence of CYP3A polymorphisms on the metabolism of tacrolimus and the clinical consequences thereof remains to be further elucidated. It is not clear whether pharmacogenetic profiling can be a useful clinical tool for identifying high risk patients and better guiding tacrolimus dosing in clinical practice [Chen and Prasad, 2018; Birdwell et al, 2015].
Preventability:	Coadministration of tacrolimus with CYP3A4 inhibitors/inducers or drugs known to be metabolized by CYP3A4-dependent pathways may warrant therapeutic drug monitoring, drug substitution, dose adjustment of the (co-administered) drug and/or close clinical monitoring. When adhering to these measures as recommended in the product label (SmPC Sections 4.2, 4.4 and 4.5), this risk and associated medical consequences can be minimized or prevented. The measures as presented in the product label are also endorsed by the COMMIT Group recommendations [Neuberger et al, 2017] and are considered to be part of routine clinical practice with regards to the management of SOT recipients within the EU. This guideline underscores the importance of anticipating and/or preventing (CYP3A4 associated) drug-drug interactions including the avoidance of food contents and herbal products interfering with hepatic CYP3A and/or intestinal CYP3A4 enzymes. This guideline also recommends clinicians to educate patients on diet content and interactions with other drugs (or some herbal products).
Impact on the risk-benefit balance of the product:	Given the narrow therapeutic index of tacrolimus and the potential for serious consequences associated with tacrolimus under-dosing (i.e., graft rejection) and over-dosing (e.g., nephrotoxicity and hepatotoxicity which could affect graft function) due to drug interactions, this important identified risk could have an impact on the risk-benefit balance.
Public health impact:	Coadministration of tacrolimus with CYP3A4 inhibitors/inducers or drugs known to be metabolized by CYP3A4-dependent pathways may affect the plasma concentration of the co-administered drug. Increases or decreased in the concentration of drugs with narrow therapeutic indices may pose a safety concern and may present a burden for national

Important Identified Risk:	Interaction with other medication and herbal drugs
	healthcare systems (e.g., due to high rate of hospital admissions and potentially fatal outcomes).

AUC: Area Under the Curve; COMMIT: Consensus on Managing Modifiable risk in Transplantation CYP3A4: Cytochrome P-450 3A4 isoenzyme; EU: European Union; MedDRA: Medical Dictionary for Regulatory Activities; SmPC: Summary of Product Characteristics; SOT: Solid Organ Transplant

Important Identified Risk:	Ventricular hypertrophy
MedDRA term(s)	High Level Group Term (HLGT) Myocardial Disorders
Potential mechanisms:	Potential mechanisms are the hypertrophic response of the myocardium secondary to hypertension and fluid overload. Hypertension is a known adverse event for tacrolimus and for other immunosuppressants such as prednisone.
Evidence source(s) and strength of evidence:	This important identified risk is based on data from tacrolimus clinical and post-marketing experience.
Characterization of the risk:	The Astellas global safety database contains a relatively small number of reported events falling under the HLGT Myocardial disorder, for which tacrolimus is reported as suspect drug or concomitant medication (n = 306 cumulatively up to 31 Dec 2019, including invalid cases), considering the product's time in the market and an estimated cumulative exposure from marketing experience of approximately 6.55 million patient-years. From the cases in which the age of the patient has been reported, 68% were in adults, the remainder was mostly from the pediatric population. From the events for which an outcome has been reported, more than half were recovered or recovering, indicating reversibility of the event. Cases are often confounded by multiple comorbidities or underlying conditions (e.g., heart disease, hypertension, diabetes mellitus, oedema, and heart transplant procedure). In many cases other cardiac events are reported concomitantly.
Risk factors and risk groups:	Risk factors include pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema.
Preventability:	High-risk patients should be monitored, particularly young children and those receiving substantial immunosuppression, using procedures such as echocardiography or ECG pre- and posttransplant. If abnormalities develop, dose reduction of tacrolimus therapy, or change of treatment to another immunosuppressive agent should be considered. Several clinical practice guidelines describe how to screen and monitor transplant patients in order to prevent and/or manage cardiovascular complications [Neuberger, 2017; Martin, 2014; Costanzo, 2010; KDIGO, 2009].
Impact on the risk-benefit balance of the product:	Reduction of the tacrolimus dose or change to another immunosuppressive agent should be considered. However, because options for immunosuppressive therapy are limited and other immunosuppressive agents also have toxicities, this may impact the risk-benefit balance.

Important Identified Risk:	**Ventricular hypertrophy**
Public health impact:	The number of reported events is limited, given the estimated cumulative exposure from marketing experience of approximately 6.55 million patient-years. Furthermore, more than half of the reported events were reversible. The public health impact is considered limited.

ECG: Electrocardiogram; HLGT: High level group term; MedDRA: Medical Dictionary for Regulatory Activities

Important Identified Risk:	**Cardiomyopathies**
MedDRA term(s)	SMQ Cardiomyopathy [narrow]
Potential mechanisms:	Cardiomyopathies are heart muscle diseases, which have been defined by their central hemodynamics and macropathology and divided into 5 major forms: dilated, hypertrophic, restrictive, right ventricular and non-classifiable cardiomyopathies [Maisch et al, 2005]. Ventricular hypertrophy or hypertrophy of the septum have been reported as cardiomyopathies. Potential mechanisms are the hypertrophic response of the myocardium secondary to hypertension and fluid overload. Hypertension is a known adverse event for tacrolimus and for other immunosuppressants such as prednisone.
Evidence source(s) and strength of evidence:	This important identified risk is based on data from tacrolimus clinical and post-marketing experience.
Characterization of the risk:	The Astellas global safety database contains a relatively small number of reported events falling under the SMQ Cardiomyopathies [narrow], for which tacrolimus is reported as suspect drug or concomitant medication (n = 262 cumulatively up to 31 Dec 2019, including invalid cases), considering the product's time in the market and an estimated cumulative exposure from marketing experience of approximately 6.55 million patient-years. From the cases in which the age of the patient has been reported, 60% were in adults, and 32% in the pediatric population. Only a minority occurred in the elderly. From the events for which an outcome has been reported, more than half were recovered or recovering, indicating reversibility of the event. Cases are often confounded by multiple comorbidities or underlying conditions (e.g., heart disease, hypertension, diabetes mellitus, oedema, and heart transplant procedure). In many cases other cardiac events are reported concomitantly.
Risk factors and risk groups:	Risk factors include pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema.

Important Identified Risk:	**Cardiomyopathies**
Preventability:	High-risk patients should be monitored, particularly young children and those receiving substantial immunosuppression, using procedures such as echocardiography or ECG pre- and posttransplant. If abnormalities develop, dose reduction of tacrolimus therapy, or change of treatment to another immunosuppressive agent should be considered. Several clinical practice guidelines describe how to screen and monitor transplant patients in order to prevent and/or manage cardiovascular complications [Neuberger, 2017; Martin, 2014; Costanzo, 2010; KDIGO, 2009].
Impact on the risk-benefit balance of the product:	Reduction of the tacrolimus dose or change to another immunosuppressive agent should be considered. However, because options for immunosuppressive therapy are limited and other immunosuppressive agents also have toxicities, this may impact the risk-benefit balance.
Public health impact:	The number of reported events is limited, given the estimated cumulative exposure from marketing experience of approximately 6.55 million patient-years. Furthermore, more than half of the reported events were reversible. The public health impact is considered limited.

ECG: Electrocardiogram; HLGT: High level group term; MedDRA: Medical Dictionary for Regulatory Activities; SMQ: Standardized MedDRA Query

Important Identified Risk:	**Use during pregnancy**
MedDRA term(s)	SMQ Pregnancy and neonatal topics [broad scope]
Potential mechanisms:	Not applicable
Evidence source(s) and strength of evidence:	This important identified risk is based on data from the tacrolimus post-marketing experience and on data from the Transplant Pregnancy Registry. This voluntary pregnancy registry was established in 1991, to study the outcomes of pregnancies in SOT recipients in North America and was expanded in 2016 allowing international participation (Transplant Pregnancy Registry International [TPRI]).
Characterization of the risk:	Human data shows that tacrolimus is able to cross the placenta. With more data becoming available from organ transplant recipients, there is no evidence of an increased risk of adverse effects on the course and outcome of pregnancy under tacrolimus treatment as compared with other immunosuppressive medicinal products. Cases of spontaneous abortion have been reported. In case of in-utero exposure, monitoring of the newborn for the potential adverse effects of tacrolimus, is recommended (in particular the effects on the kidneys). There is a risk for premature delivery (<37 week) as well as for hyperkalemia in the newborn which, however, normalizes spontaneously.
Risk factors and risk groups:	Not applicable.
Preventability:	Not applicable.
Impact on the risk-benefit balance of the product:	A pregnancy, after SOT, is considered a high-risk pregnancy and should be monitored by both an obstetrician and the transplant physician. Also, the pregnancy should be diagnosed as early in pregnancy as possible.
Public health impact:	Although the outcome of live births is favorable, the risks of maternal and fetal complications are high in transplant recipients.

MedDRA: Medical Dictionary for Regulatory Activities; SMQ: Standardized MedDRA query; SOT: Solid Organ Transplantation; TPRI: Transplant Pregnancy Registry International.

Important Identified Risk:	**Use during lactation**
MedDRA term(s)	SMQ Neonatal exposures via breast milk
Potential mechanisms:	Not applicable
Evidence source(s) and strength of evidence:	This important identified risk is based on data from the tacrolimus post-marketing experience and on data from the Transplant Pregnancy Registry. This voluntary pregnancy registry was established in 1991, to study the outcomes of pregnancies in SOT recipients in North America and was expanded in 2016, allowing international participation (Transplant Pregnancy Registry International [TPRI]).
Characterization of the risk:	Human data demonstrates that tacrolimus is excreted into breast milk. Detrimental effects on the newborn cannot be excluded.
Risk factors and risk groups:	Not applicable.
Preventability:	Not applicable.
Impact on the risk-benefit balance of the product:	Overall, the number of cases describing breastfeeding during treatment with tacrolimus is low considering the greater than 20 years of post-marketing experience of tacrolimus. There is limited information on the long-term follow-up (ranging from about 6 months to 5½ years) of breast-fed infants exposed to tacrolimus through breast-feeding. The available data from the Astellas global safety database, TPRI and published literature are not suggestive of any safety issues associated with breastfeeding in mothers treated with tacrolimus or their breast-fed infants.
Public health impact:	The public health impact is expected to be negligible.

MedDRA: Medical Dictionary for Regulatory Activities; SMQ: Standardized MedDRA query; SOT: Solid Organ Transplant; TPRI: Transplant Pregnancy Registry International.

SVII.3.2 Presentation of the missing information

This section is not applicable.

PART II: MODULE SVIII. SUMMARY OF THE SAFETY CONCERNS

Data-lock point for this Module	31 Dec 2019
Version when Module last updated	3.2

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Malignant neoplasms • Serious infections and reactivation of pre-existing infections • Medication errors resulting in under or over exposure to tacrolimus-containing medicinal products with potentially serious consequences • Interaction with other medication and herbal drugs • Ventricular hypertrophy • Cardiomyopathies • Use during pregnancy • Use during lactation
Important potential risks	• None
Missing information	• None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

Data-lock point for this Module	22 Feb 2024
Version when Module last updated	5.2

III.1 Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific Adverse Reaction Follow-up Questionnaires:

Description	Purpose	Safety concern(s) addressed
Targeted follow-up questionnaire for medication errors involving unintentional or unsupervised switching between systemic tacrolimus formulations.	Monitoring, standardized collection, and documentation of medication switch errors to recognize patterns and impact on treated patients.	Medication errors resulting in under or over exposure to tacrolimus-containing medicinal products with potentially serious consequences

Adverse event follow-up questionnaires are provided in [Annex 4]

Other Forms of Routine Pharmacovigilance Activities:

Activity	Objective(s)/Description	Milestone(s)
Monitoring Targeted Medical Events (TMEs)	Monitoring TMEs as part of signal detection, applicable for the safety concerns: - Malignant neoplasms - Serious infections and reactivation of pre-existing infections - Medication Errors - Interaction with other medication and herbal drugs - Ventricular hypertrophy - Cardiomyopathies - Use during Pregnancy - Use during Lactation	Quarterly monitoring

TME: Targeted Medical Event

III.2 Additional pharmacovigilance activities

Additional Pharmacovigilance Activities

Study short name and title	**Feasibility assessment of conducting a non-interventional post-authorization safety study (NI-PASS) of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from available secondary use data sources to replicate the Transplant Pregnancy Registry International (TPRI) study**
Rationale and objectives	Rationale: In view of the limitations of the TPRI study (refer to the clinical safety report appended with this RMP for details) as well as the importance of data regarding the use of tacrolimus in pregnancy, the MAH is asked to provide a critical analysis of the feasibility of using alternative data sources to complement the TPRI study outcomes of pregnancy in transplant recipients exposed to tacrolimus and in infants exposed to tacrolimus in utero. In February 2021, the Committee for Medicinal Products for Human Use (CHMP) of the EMA adopted a positive opinion recommending the implementation of the EU-RMP version 3.2 for Advagraf, Modigraf and Prograf and requested Astellas to submit within 6 months a critical analysis of the feasibility of using alternative data sources to complement TPRI study outcomes as a post-authorization measure. Astellas conducted a feasibility assessment that aimed to investigate the availability of relevant data in the United Kingdom (UK), Canada, Nordic countries, and Italy, and to inform a decision on the choice of data sources if a full study is considered viable. In July 2021, Astellas submitted to PRAC the report of this qualitative feasibility assessment. In March 2023, the MAH received the CHMP endorsement of the Assessment Report of this feasibility assessment stating that this step of the post authorization measure is fulfilled. Activities to prepare for further feasibility assessment were started by the MAH, aiming to assess the potential of selected data sources in providing an adequate sample size to conduct a potential safety study evaluating pregnancy outcomes after exposure to tacrolimus and alternative immunosuppressants. In Nov 2023, the MAH submitted a progress report of this feasibility assessment. In Feb 2024, the MAH received the CHMP adoption of conclusions. The following research questions will be addressed if it is deemed feasible based on the feasibility assessment outcome including the patient counts. Research questions: 1. What are the outcomes of pregnancies in female transplant recipients using tacrolimus? 2. What are the outcomes in children exposed to tacrolimus via breastfeeding?

Study short name and title	**Feasibility assessment of conducting a non-interventional post-authorization safety study (NI-PASS) of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from available secondary use data sources to replicate the Transplant Pregnancy Registry International (TPRI) study**
	3. What are the outcomes of pregnancies fathered by male transplant recipients exposed to tacrolimus? 4. What are the maternal outcomes during pregnancy in female transplant recipients using tacrolimus? Objectives for the feasibility assessment: 1. To estimate, in each of the data sources, the count of pregnancies in which the mother is a transplant recipient who had an exposure before conception or during pregnancy to: o Tacrolimus o Alternative immunosuppressants 2. To estimate, in each of the data sources, the count of pregnancies in which the biological father is a transplant recipient who had an exposure before conception to: o Tacrolimus o Alternative immunosuppressants 3. To describe the type of transplantation (renal, liver, heart, or other) among the transplant recipients related to the pregnancies assessed in the previous objectives 4. To describe the timing of maternal exposure to tacrolimus or alternative immunosuppressants before conception and during pregnancy
Design	This will be a non-interventional multi-country feasibility assessment using longitudinal secondary data from large data sources in Finland, Norway, Sweden, the United Kingdom (UK), Denmark and France to assess exposure to tacrolimus and alternative immunosuppressants before conception and during pregnancy among transplant recipients, considering both maternal and paternal exposure. With pregnancy as the unit of analysis, the results will be counts of pregnancies with maternal and paternal exposure to tacrolimus and alternative immunosuppressants, considering the inclusion and exclusion criteria. The index date for each pregnancy will be defined as the date of conception and will determine the start of the observation period for each individual report of pregnancy.
Study population	Inclusion criteria: 1. Women and men linked, as biological mothers or fathers, to a record of any pregnancy starting during the inclusion period.

Study short name and title	Feasibility assessment of conducting a non-interventional post-authorization safety study (NI-PASS) of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from available secondary use data sources to replicate the Transplant Pregnancy Registry International (TPRI) study
	2. A record indicative of an organ transplant procedure, including renal, liver, heart, or other transplants, reported during the pre-index period. This inclusion criterion will be based on diagnosis codes. 3. Having at least one record of tacrolimus or an alternative immunosuppressant drug: o Within 6 weeks prior to index date or during the post-index period, for mothers o Within 6 weeks prior to index date, for fathers 4. Availability of information on transplants for a minimum of 12 months before the index date. 5. Availability of information on exposure to tacrolimus, alternative immunosuppressants, and mycophenolic acid (MPA) for: o A minimum of 6 weeks for mothers before the index date o A minimum of 90 days for fathers before the index date <u>Exclusion criterion</u> Due to its known teratogenic potential, exposure to MPA will be an exclusion criterion: 1. Within 6 weeks prior to index date or during the post-index period, for mothers 2. Within 90 days prior to index date, for fathers
Milestones	Progress report endorsed by CHMP/EMA: 22 Feb 2024. Final report planned: Sep 2025

CHMP: Committee for medicinal products for human use; EMA: European Medicines Agency; EU: European Union; MAH: Marketing authorization holder; MPA: Mycophenolic acid; NI-PASS: Non-Interventional Post-Authorization Safety Study; PRAC: Pharmacovigilance Risk Assessment Committee; RMP: Risk Management Plan; TPRI: Transplant Pregnancy Registry International; UK: United Kingdom.

III.3 Summary table of additional pharmacovigilance activities

Table Part III. 1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				

Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Ongoing	To assess the potential of selected data sources in providing adequate sample size to conduct a potential safety study evaluating pregnancy outcomes after exposure to tacrolimus and alternative immunosuppressants	• Use during pregnancy • Use during lactation	Progress report endorsed by CHMP/EMA Final study report planned	22 Feb 2024 Sep 2025

CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Data-lock point for this Module	31 Dec 2019
Version when Module last updated	3.0

Table Part IV.1: Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of The Marketing Authorization Or That Are Specific Obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorization				
Not Applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not Applicable				

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

Data-lock point for this Module	14 Feb 2023
Version when Module last updated	5.0

V.1 Routine risk minimization measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Malignant neoplasms	Routine risk communication: • SmPC Section 4.8 • PL Sections 2 and 4 Routine risk minimization activities, recommending specific clinical measures to address the risk: • Warning in SmPC Section 4.4 that concomitant use of tacrolimus and anti-lymphocyte treatment increases the risk of Epstein-Barr-Virus (EBV)-associated lymphoproliferative disorders. • Recommendation in SmPC Section 4.4 to limit the exposure to sunlight owing to the potential risk of malignant skin changes. • Recommendation in SmPC Section 4.4 to ascertain, in EBV-Viral Capsid Antigen (VCA)-negative patients, EBV-VCA serology before initiation of tacrolimus therapy and a recommendation for careful monitoring with EBV-PCR. Other routine risk minimization measures beyond the Product Information: • Tacrolimus is a ‘prescription only medicine’ and requires careful monitoring by adequately qualified and equipped personnel. Tacrolimus should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients (SmPC Section 4.2).
Serious infections and reactivation of pre-existing infections	Routine risk communication: • SmPC Sections 4.8 • PL Section 4 Routine risk minimization activities, recommending specific clinical measures to address the risk: • Warning in SmPC Section 4.4 about the increased risk for serious infections or reactivation of infections, often related to a high total immunosuppressive burden, which may lead to serious or fatal conditions.

Safety concern	Routine risk minimization activities
	• Recommendation in SmPC Section 4.4 to consider, in the differential diagnosis in immunosuppressed patients with deteriorating hepatic or renal function or neurological symptoms, that these conditions may be associated with serious infections or reactivation of infections. • Recommendation in SmPC Section 4.4 for prevention and management of infections in accordance with appropriate clinical guidance. • Recommendations in SmPC Section 4.9 in case of accidental overdose. Other routine risk minimization measures beyond the Product Information: Tacrolimus is a 'prescription only medicine' and requires careful monitoring by adequately qualified and equipped personnel. Tacrolimus should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients (SmPC Section 4.2).
Medication errors resulting in under or over exposure to tacrolimus-containing medicinal products with potentially serious consequences	Routine risk communication: • SmPC Sections 4.2 and 4.8 • PL Section 3 Routine risk minimization activities, recommending specific clinical measures to address the risk: • Recommendation in SmPC Section 4.4 for maintaining patients on a single formulation and to alter formulations or regimen only under the close supervision of a transplant specialist. • Recommendation in SmPC Section 4.2 about the need for therapeutic drug monitoring and dose adjustments, following conversion to any alternative formulation, to maintain systemic exposure to tacrolimus. Other routine risk minimization measures beyond the Product Information: • Tacrolimus is a 'prescription only medicine' and requires careful monitoring by adequately qualified and equipped personnel. Tacrolimus should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients (SmPC Section 4.2).

Interaction with other medication and herbal drugs	Routine risk communication: • PL Section 2 Routine risk minimization activities, recommending specific clinical measures to address the risk: • Recommendation in SmPC Section 4.2 about monitoring of blood trough levels of tacrolimus following co-administration of substances which may alter tacrolimus whole blood concentrations. • Recommendation in SmPC Section 4.4 to closely monitor tacrolimus blood levels, and to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure, when used concomitantly with inhibitors or inducers of CYP3A4. • Recommendation in SmPC Section 4.4 to avoid concomitant use with herbal preparations. • Recommendation in SmPC Sections 4.4 and 4.5 to avoid concomitant use with ciclosporin or potassium-sparing diuretics. • Warning in SmPC Sections 4.4 and 4.5 that certain combinations of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects. • Recommendation in SmPC Section 4.5 to closely monitor tacrolimus blood levels, as well as QT prolongation (with ECG), renal function and other side effects, whenever substances which have the potential to alter CYP3A4 metabolism or otherwise influence tacrolimus blood levels are used concomitantly. • Recommendation in SmPC Section 4.5 about other (not related to CYP3A4) interactions potentially leading to increased tacrolimus blood levels. • Recommendation in SmPC Section 4.5 about the effect of tacrolimus on the metabolism of other medicinal products because tacrolimus is a known CYP3A4 inhibitor. • Recommendation in SmPC Section 4.5 about the need of therapeutic drug monitoring of mycophenolic acid (MPA) when switching combination therapy from ciclosporin/MPA to tacrolimus/MPA or vice versa because ciclosporin interferes with the enterohepatic recirculation of MPA. • Recommendation in Sections 4.4 and 4.5 to avoid the use of live attenuated vaccines. Other routine risk minimization measures beyond the Product Information: • Tacrolimus is a ‘prescription only medicine’ and requires careful monitoring by adequately qualified and equipped personnel. Tacrolimus should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians

Safety concern	Routine risk minimization activities
	experienced in immunosuppressive therapy and the management of transplant patients (SmPC Section 4.2).
Ventricular hypertrophy	Routine risk communication: • SmPC Section 4.8 • PL Section 4 Routine risk minimization activities, recommending specific clinical measures to address the risk: • Recommendation in SmPC Section 4.4 to monitor high-risk patients, particularly young children and those receiving substantial immunosuppression, using such procedures as echocardiography or ECG pre- and post-transplant (e.g., initially at 3 months and then at 9 to 12 months) and if abnormalities develop, to consider dose reduction of tacrolimus therapy, or change of treatment to another immunosuppressive agent. Other routine risk minimization measures beyond the Product Information: Tacrolimus is a 'prescription only medicine' and requires careful monitoring by adequately qualified and equipped personnel. Tacrolimus should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients (SmPC Section 4.2).
Cardiomyopathies	Routine risk communication: • SmPC Section 4.8 • PL Section 4 Routine risk minimization activities, recommending specific clinical measures to address the risk: • Recommendation in SmPC Section 4.4 to monitor high-risk patients, particularly young children and those receiving substantial immunosuppression, using such procedures as echocardiography or ECG pre- and post-transplant (e.g., initially at 3 months and then at 9 to 12 months) and if abnormalities develop, to consider dose reduction of tacrolimus therapy, or change of treatment to another immunosuppressive agent. Other routine risk minimization measures beyond the Product Information: Tacrolimus is a 'prescription only medicine' and requires careful monitoring by adequately qualified and equipped personnel. Tacrolimus should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in

Safety concern	Routine risk minimization activities
	immunosuppressive therapy and the management of transplant patients (SmPC Section 4.2).
Use during pregnancy	Routine risk communication: • SmPC Section 4.6 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation in SmPC Section 4.6 to monitor the newborn for the potential adverse effects of tacrolimus in case of in-utero exposure. • Recommendation in SmPC Section 4.6 that tacrolimus treatment can be considered in pregnant women, when there is no safer alternative and when the perceived benefit justifies the potential risk to the fetus. Other routine risk minimization measures beyond the Product Information: Tacrolimus is a 'prescription only medicine' and requires careful monitoring by adequately qualified and equipped personnel. Tacrolimus should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients (SmPC Section 4.2).
Use during lactation	Routine risk communication: • SmPC Section 4.6 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation in SmPC Section 4.6 that women should not breast-feed whilst receiving tacrolimus. Other routine risk minimization measures beyond the Product Information: Tacrolimus is a 'prescription only medicine' and requires careful monitoring by adequately qualified and equipped personnel. Tacrolimus should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients (SmPC Section 4.2).

CYP3A4: Cytochrome P-450 3A4; EBV: Epstein-Barr Virus; ECG: Electrocardiogram; MPA: Mycophenolic Acid; PCR: Polymerase Chain Reaction; PL: Package leaflet; SmPC: Summary of Product Characteristics. VCA: Viral Capsid Antigen

V.2 Additional risk minimization measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.2.1 Removal of additional risk minimization activities

Activity	Safety concern(s) addressed	Rationale for the removal of additional risk minimization activity
DHPC (Direct communication of Advagraf/Prograf medication errors was sent to HCPs across the EEA in 2008)	Medication errors resulting in under or over exposure to tacrolimus-containing medicinal products with potentially serious consequences: There is a potential for Advagraf-Prograf medication error. Following marketing authorization approval in the EU, Advagraf-Prograf medication errors have been reported. This resulted in the MAH to conduct a detailed root cause analysis and implementation of risk minimization activities since 2008.	There has been a downward trend in the reporting of Advagraf – Prograf medication errors since the implementation of risk minimization measures in Dec 2008 (i.e., from 72 cases in the PSUR reporting interval 01 Apr 2008- 31 Mar 2009 to 25 cases in the PSUR reporting interval 01 Apr 2018 – 31 Mar 2019). Routine risk minimization is considered sufficient. The SmPC contains a warning about medication errors and recommendations to maintain the patients on a single formulation of tacrolimus and to have the alterations in formulations or regimen take place only under the close supervision of a transplant specialist. Details about reported medication errors are presented in the periodic safety update reports.

DHPC: Direct Healthcare Professional Communication; EEA: European Economic Area; EU: European Union; HCP: Healthcare Professionals; MAH: Market Authorization Holder; PSUR: Periodic Safety Update Report; SmPC: Summary of Product Characteristics.

V.3 Summary of risk minimization measures

Table Part V.3: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Malignant neoplasms	Routine risk minimization measures: • SmPC Section 4.8 • SmPC Section 4.4 in which a warning is included that concomitant use of tacrolimus and anti-lymphocyte treatment increases the risk of Epstein-Barr-Virus (EBV)-associated lymphoproliferative disorders. • SmPC Section 4.4 in which recommendations are given to limit the exposure to sunlight • SmPC Section 4.4 in which a recommendation is given to ascertain, in EBV- Viral Capsid Antigen (VCA)-negative patients, EBV-VCA serology before initiation of tacrolimus therapy and a recommendation for careful monitoring with EBV-PCR • PL Sections 2 and 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Serious infections and reactivation of pre-existing infections	Routine risk minimization measures: • SmPC Section 4.8 • SmPC Section 4.4 including a warning in SmPC Section 4.4 about the increased risk for serious infections or reactivation of infections, often related to a high total immunosuppressive burden, which may lead to serious or fatal conditions. • SmPC Section 4.4 in which the recommendation is given to consider, in the differential diagnosis in immunosuppressed patients with deteriorating hepatic or renal function or neurological symptoms, that these conditions may be associated with serious infections or	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	reactivation of infections. • SmPC Section 4.4 in which the recommendation is given for prevention and management of infections in accordance with appropriate clinical guidance. • SmPC Section 4.9 in which recommendations are given in case of accidental overdose. • PL Section 4 Additional risk minimization measures: • None	
Medication errors resulting in under or over exposure to tacrolimus-containing medicinal products with potentially serious consequences	Routine risk minimization measures: • SmPC Sections 4.2 and 4.8 • SmPC Section 4.4, in which medication errors are addressed and recommendations are given to maintain patients on a single formulation of tacrolimus and to alter formulations or regimen only under the close supervision of a transplant specialist • SmPC Section 4.2, in which recommendations are given about the need for therapeutic drug monitoring and dose adjustments following conversion to any alternative formulation. • PL Section 3 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted follow-up questionnaire for ongoing monitoring of medication errors Additional pharmacovigilance activities: • None
Interaction with other medication and herbal drugs	Routine risk minimization measures: • SmPC Section 4.2 in which a recommendation is given about monitoring of blood trough levels of tacrolimus following co-administration of substances which may alter tacrolimus whole blood concentrations. • SmPC Section 4.4 in which a recommendation is given to closely monitor tacrolimus blood levels, and to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure, when used concomitantly with inhibitors	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	or inducers of CYP3A4. • SmPC Section 4.4 in which a recommendation is given to avoid concomitant use with herbal preparations. • SmPC Sections 4.4 and 4.5 in which a recommendation is given to avoid concomitant use with ciclosporin or potassium-sparing diuretics. • SmPC Sections 4.4 and 4.5 in which a warning is included that certain combinations of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects. • SmPC Section 4.5 in which a recommendation is given to closely monitor tacrolimus blood levels, as well as QT prolongation (with ECG), renal function and other side effects, whenever substances which have the potential to alter CYP3A4 metabolism or otherwise influence tacrolimus blood levels are used concomitantly. • SmPC Section 4.5 in which a recommendation is given about other (not related to CYP3A4) interactions potentially leading to increased tacrolimus blood levels. • SmPC Section 4.5 in which a recommendation is given about the effect of tacrolimus on the metabolism of other medicinal products because tacrolimus is a known CYP3A4 inhibitor. • SmPC Section 4.5 in which a recommendation is given about the need of therapeutic drug monitoring of mycophenolic acid (MPA) when switching combination therapy from ciclosporin/MPA to tacrolimus/MPA or vice versa because ciclosporin interferes with the enterohepatic recirculation of MPA. • SmPC Sections 4.4 and 4.5 in which a recommendation is given to avoid the use of live attenuated vaccines.	

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• PL Section 2 Additional risk minimization measures: • None	
Ventricular hypertrophy	Routine risk minimization measures: • SmPC Section 4.4 in which recommendations are given to monitor high-risk patients, and if abnormalities develop, to consider dose reduction of tacrolimus therapy, or change of treatment to another immunosuppressive agent. • PL Section 4 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Cardiomyopathies	Routine risk minimization measures: • SmPC Section 4.4 in which recommendations are given to monitor high-risk patients, and if abnormalities develop, to consider dose reduction of tacrolimus therapy, or change of treatment to another immunosuppressive agent. • PL Section 4 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: None
Use during pregnancy	Routine risk minimization measures: • SmPC Section 4.6, in which recommendation is given to monitor the newborn for the potential adverse effects of tacrolimus in case of in-utero exposure • SmPC Section 4.6 in which recommendation is given that tacrolimus treatment can be considered in pregnant women, when there is no safer alternative and when the perceived benefit justifies the potential risk to the fetus. • PL Section 2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: Feasibility assessment – Feasibility assessment of conducting a non-interventional post-authorization safety study (NI-PASS) of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from available secondary use data sources to replicate the Transplant Pregnancy Registry International (TPRI) study

Safety concern	Risk minimization measures	Pharmacovigilance activities
Use during lactation	Routine risk minimization measures: • SmPC Section 4.6, in which recommendation is given that women should not breast-feed whilst receiving tacrolimus. • PL Section 2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: Feasibility assessment – Feasibility assessment of conducting a non-interventional post-authorization safety study (NI-PASS) of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from available secondary use data sources to replicate the Transplant Pregnancy Registry International (TPRI) study.

CYP3A4: Cytochrome P-450 3A4; EBV-VCA: Epstein-Barr-Virus/Viral Capsid Antigen; ECG: Electrocardiogram; MPA: Mycophenolic Acid; NI-PASS: Non-interventional Post Authorization Safety Study; PCR: Polymerase Chain Reaction; PL: Package leaflet; SmPC: Summary of Product Characteristics; TPRI: Transplant Pregnancy Registry International

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Data-lock point for this Module	14 Feb 2023
Version when Module last updated	5.0

Summary of risk management plan for Prograf™, Advagraf™, Modigraf™ (Systemic Tacrolimus)

This is a summary of the RMP for Prograf™, Advagraf™, and Modigraf™. The RMP details important risks of Prograf, Advagraf, and Modigraf, how these risks can be minimized, and how more information will be obtained about these risks and uncertainties (missing information).

Prograf, Advagraf, and Modigraf SmPCs and its package leaflets, give essential information to healthcare professionals and patients on how it should be used.

In the EU, Prograf capsules and concentrate for infusion are authorized via mutual recognition procedure/national procedures; consequently, there is no European Public Assessment Report (EPAR) for Prograf.

Advagraf and Modigraf are authorized via centralized procedures.

This summary of the RMP for Prograf, Advagraf and Modigraf should be read in the context of all this information, including, for the centrally authorized products Advagraf and Modigraf, the assessment report of the evaluation and its plain-language summary, all of which is part of the EPAR.

Important new concerns or changes to the current ones will be included in updates of Prograf, Advagraf, and Modigraf's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Prograf is authorized for prophylaxis of transplant rejection in liver, kidney or heart allograft recipients; and for the treatment of allograft rejection, resistant to treatment with other immunosuppressive medicinal products (see SmPC for the full indication). It contains tacrolimus monohydrate as the active substance, and it is given orally or is available as a concentrate solution for infusion.

Advagraf is authorized for prophylaxis of transplant rejection in adult kidney or liver allograft recipients; and for the treatment of allograft rejection, resistant to treatment with other immunosuppressive medicinal products in adult patients (refer to SmPC for the full indication). It contains tacrolimus monohydrate as the active substance, and it is given orally.

Modigraf is authorized for prophylaxis of transplant rejection in liver, kidney or heart allograft recipients; and for the treatment of allograft rejection, resistant to treatment with other immunosuppressive medicinal products (see SmPC for the full indication). It contains tacrolimus monohydrate as the active substance, and it is given orally.

Further information about the evaluation of the centrally authorized products Advagraf and Modigraf benefits can be found in Advagraf's and Modigraf's EPARs, including in its

plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/advagraf and https://www.ema.europa.eu/en/medicines/human/EPAR/modigraf.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Prograf, Advagraf, and Modigraf, together with measures to minimize such risks and the proposed studies for learning more about Prograf, Advagraf, and Modigraf's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and the SmPC, addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen as to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute the routine risk minimization measures.

In addition to these measures, information about the adverse reactions is collected continuously and is regularly analyzed, including PSUR assessment, so that immediate action can be taken if necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Prograf, Advagraf, and Modigraf are those risks that need special risk management activities to further investigate or minimize them, so that the medicinal product can be safely administered or taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Prograf, Advagraf, and Modigraf. Potential risks are concerns for which an association with the use of this medicine is possible, based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information regarding the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Malignant neoplasms • Serious infections and reactivation of pre-existing infections • Medication errors resulting in under or over exposure to tacrolimus-containing medicinal products with potentially serious consequences • Interaction with other medication and herbal drugs • Ventricular hypertrophy • Cardiomyopathies • Use during pregnancy • Use during lactation
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

Important Identified risk: Malignant neoplasms	
Evidence for linking the risk to the medicine	The increased risk in transplant recipients for developing cancer has been well described in the literature and Clinical Practice Guidelines and is also based on data from tacrolimus post-marketing experience.
Risk factors and risk groups	Risk factors for posttransplant malignancy include traditional risk factors such as advancing age, smoking, drinking alcohol, obesity, sun exposure, and family history, and risk factors that are unique to the transplant population, including immunosuppression, oncogenic viral infections, and disease-specific associations (e.g., factors related to end-stage organ disease or dialysis in the case of kidney transplant recipients) [Rossi and Klein, 2019; Acuna, 2018].
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 • SmPC Section 4.4 in which a warning is included that concomitant use of tacrolimus and anti-lymphocyte treatment increases the risk of Epstein-Barr-Virus (EBV)-associated lymphoproliferative disorders. • SmPC Section 4.4 in which recommendations are given to limit the exposure to sunlight • SmPC Section 4.4 in which a recommendation is given to ascertain, in EBV- Viral Capsid Antigen (VCA)-negative patients, EBV-VCA serology before initiation of tacrolimus therapy and a recommendation for careful monitoring with EBV-PCR • PL Sections 2 and 4 Additional risk minimization measures:

	• None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

EBV: Epstein-Barr-Virus; PL: Package Leaflet; PCR: Polymerase Chain Reaction; SmPC: Summary of Product Characteristics; VCA: Viral Capsid Antigen

Important Identified risk: Serious infections and reactivation of pre-existing infections	
Evidence for linking the risk to the medicine	This important identified risk has been well described in the literature and Clinical Practice Guidelines and is also based on data from tacrolimus post-marketing experience.
Risk factors and risk groups	Increased risk and severity of infection in kidney transplant recipients are explained by many factors, including the recipient's condition, such as surgical complications, or the use of indwelling catheters; the possibility of transmission of infection from donor to recipient; overimmunosuppression; active smoking; and obesity, etc. Viral infections in kidney transplant recipients, which occur more frequently during the first few months, are most likely in the context of greater immunosuppression. Furthermore, recipient age is often a significant risk factor for bacterial infections, but not viral/fungal infections. Type of immunosuppressive agent such as use of induction therapy with antithymocyte globulin is also associated with viral infection. The relationship between bacterial infection in kidney transplant recipients and overimmunosuppression is well established. However, in many cases, there are additional identifiable risk factors for bacterial infection, including surgical complications, intravenous or urinary catheters, urinary retention or vesicoureteral reflux. Patients with a tuberculin purified protein derivative-positive skin test or a positive IFN-γ release assay for tuberculosis before transplantation are also at increased risk of *Mycobacterium tuberculosis* infection after transplantation [Neuberger, 2017].
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 • SmPC Section 4.4 including a warning in SmPC Section 4.4 about the increased risk for serious infections or reactivation of infections, often related to a high total immunosuppressive burden, which may lead to serious or fatal conditions. • SmPC Section 4.4 in which the recommendation is given to consider, in the differential diagnosis in immunosuppressed patients with deteriorating hepatic or renal function or neurological symptoms, that these conditions may be associated with serious infections or reactivation of infections. • SmPC Section 4.4 in which the recommendation is given for prevention and management of infections in accordance with

	appropriate clinical guidance. • SmPC Section 4.9 in which recommendations are given in case of accidental overdose. • PL Section 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

IFN: Interferon; PL: Package Leaflet; SmPC: Summary of Product Characteristics

Important Identified risk: Medication errors resulting in under or over exposure to tacrolimus-containing medicinal products with potentially serious consequences	
Evidence for linking the risk to the medicine	This important identified risk is based on data from tacrolimus post-marketing experience.
Risk factors and risk groups	A systematic review was published in 2018; this review investigated the epidemiology of medication errors and error-related adverse events in adults, in primary care, ambulatory care and patients' homes. Risk factors for medication errors listed in this 2018 review, related to patients, healthcare professionals and/or medications are listed below [Assiri et al, 2018]. Patient related risk factors for the development of medication errors: polypharmacy, increased age, number of diseases or comorbidities, female gender, low level of education, hospital admission and middle family income. Risk factors related to healthcare professionals for the development of medication errors: more than one physician involved in their care, general practice (GP), age ≥51 years, male GP, frequent changes in prescription, not considering the prescription of other physicians, inconsistency in the information and outpatient clinic visits Medication related risk factors for the development of medication errors: multiple medication storage locations used, expired medication present, discontinued medication repeats retained, hoarding of medications, therapeutic duplication, no medication administration routine, poor adherence and patients confused by generic and trade names.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.2 and 4.8 • SmPC Section 4.4, in which medication errors are addressed and recommendations are given to maintain patients on a single formulation of tacrolimus and to alter formulations or regimen only under the close supervision of a transplant specialist • SmPC Section 4.2 in which recommendations are given about the need for therapeutic drug monitoring and dose

Important Identified risk: Medication errors resulting in under or over exposure to tacrolimus-containing medicinal products with potentially serious consequences	
	adjustments following conversion to any alternative formulation. • PL Section 3 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

GP: General Practice; PL: Package Leaflet; SmPC: Summary of Product Characteristics

Important Identified risk: Interaction with other medication and herbal drugs	
Evidence for linking the risk to the medicine	This important identified risk has been well described in drug interaction studies, literature and is also based on data from tacrolimus post-marketing experience.
Risk factors and risk groups	Particularly patients that use tacrolimus and require medications or herbal remedies which are strong CYP3A4 inhibitors (e.g., such as telaprevir, boceprevir, ritonavir, ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin) or inducers (e.g., such as rifampicin, rifabutin) are at risk. Genetic CYP3A polymorphisms may have an impact on drug metabolism and a person's ability to metabolize certain drugs can be increased ("fast" metabolizers) or decreased ("poor" metabolizers). To date, the influence of CYP3A polymorphisms on the metabolism of tacrolimus and clinical consequences thereof remains to be further elucidated. It is not clear whether pharmacogenetic profiling can be a useful clinical tool for identifying high risk patients and better guiding tacrolimus dosing in clinical practice [Chen & Prasad, 2018; Birdwell et al, 2015].
Risk minimization measures	• Routine risk minimization measures: • SmPC Section 4.2 in which a recommendation is given about monitoring of blood trough levels of tacrolimus following co-administration of substances which may alter tacrolimus whole blood concentrations. • SmPC Section 4.4 in which a recommendation is given to closely monitor tacrolimus blood levels, and to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure, when used concomitantly with inhibitors or inducers of CYP3A4. • SmPC Sections 4.4 in which a recommendation is given to avoid concomitant use with herbal preparations. • SmPC Sections 4.4 and 4.5 in which a recommendation is given to avoid concomitant use with ciclosporin or potassium-sparing diuretics. • SmPC Sections 4.4 and 4.5 in which a warning is included

Important Identified risk: Interaction with other medication and herbal drugs	
	that certain combinations of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects.
Risk minimization measures	• SmPC Section 4.5 in which a recommendation is given to closely monitor tacrolimus blood levels, as well as QT prolongation (with ECG), renal function and other side effects, whenever substances which have the potential to alter CYP3A4 metabolism or otherwise influence tacrolimus blood levels are used concomitantly. • SmPC Section 4.5 in which a recommendation is given about other (not related to CYP3A4) interactions potentially leading to increased tacrolimus blood levels. • SmPC Section 4.5 in which a recommendation is given about the effect of tacrolimus on the metabolism of other medicinal products because tacrolimus is a known CYP3A4 inhibitor. • SmPC Section 4.5 in which a recommendation is given about the need of therapeutic drug monitoring of mycophenolic acid (MPA) when switching combination therapy from ciclosporin/MPA to tacrolimus/MPA or vice versa because ciclosporin interferes with the enterohepatic recirculation of MPA. • SmPC Sections 4.4 and 4.5 in which a recommendation is given to avoid the use of live attenuated vaccines. • PL Section 2 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

CYP3A4: Cytochrome P-450 3A4; ECG: Electrocardiogram; MPA: Mycophenolic Acid; PL: Package Leaflet; SmPC: Summary of Product Characteristics

Important Identified risk: Ventricular hypertrophy	
Evidence for linking the risk to the medicine	This important identified risk is based on data from tacrolimus clinical and post-marketing experience.
Risk factors and risk groups	Risk factors include pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 in which recommendations are given to monitor high-risk patients, and if abnormalities develop, to consider dose reduction of tacrolimus therapy, or change of treatment to another immunosuppressive agent. • PL Section 4

	Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

PL: Package Leaflet; SmPC: Summary of Product Characteristics

Important Identified risk: Cardiomyopathies	
Evidence for linking the risk to the medicine	This important identified risk is based on data from tacrolimus clinical and post-marketing experience.
Risk factors and risk groups	Risk factors include pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 in which recommendations are given to monitor high-risk patients, and if abnormalities develop, to consider dose reduction of tacrolimus therapy, or change of treatment to another immunosuppressive agent. • PL Section 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

PL: Package Leaflet; SmPC: Summary of Product Characteristics

Important Identified risk: Use during pregnancy	
Evidence for linking the risk to the medicine	This important identified risk is based on data from tacrolimus post-marketing experience and on data from the Transplant Pregnancy Registry. This voluntary pregnancy registry was established in 1991 to study the outcomes of pregnancies in SOT recipients in North America and was expanded in 2016, allowing international participation (Transplant Pregnancy Registry International [TPRI]).
Risk factors and risk groups	Not applicable.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.6, in which recommendation is given to monitor the newborn for the potential adverse effects of tacrolimus in case of in utero exposure. • SmPC Section 4.6, in which recommendation is given that tacrolimus treatment can be considered in pregnant women, when there is no safer alternative and when the perceived benefit justifies the potential risk to the fetus. • PL Section 2

	Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Feasibility assessment – Feasibility assessment of conducting a non-interventional post-authorization safety study (NI-PASS) of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from available secondary use data sources to replicate the Transplant Pregnancy Registry International (TPRI) study See [Section II.C] of this summary for an overview of the post-authorization development plan.

NI-PASS: Non-interventional Post Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics; SOT: Solid Organ Transplant; TPRI: Transplant Pregnancy Registry International.

Important Identified risk: Use during lactation	
Evidence for linking the risk to the medicine	This important identified risk is based on data from tacrolimus post-marketing experience and on data from the Transplant Pregnancy Registry. This voluntary pregnancy registry was established in 1991 to study the outcomes of pregnancies in SOT recipients in North America and was expanded in 2016 allowing international participation (Transplant Pregnancy Registry International [TPRI]).
Risk factors and risk groups	Not applicable.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.6, in which recommendation is given that women should not breast-feed whilst receiving tacrolimus. • PL Section 2 Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Feasibility assessment – Feasibility assessment of conducting a non-interventional post-authorisation safety study (NI-PASS) of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from available secondary use data sources to replicate

	the Transplant Pregnancy Registry International (TPRI) study See [Section II.C] of this summary for an overview of the post-authorization development plan.

NI-PASS: Non-interventional Post Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics; SOT: Solid Organ Transplant; TPRI: Transplant Pregnancy Registry International.

II.C Post authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies that are conditions of the marketing authorization or specific obligation of Prograf, Advagraf, and Modigraf.

II.C.2 Other studies in post authorization development plan

Feasibility assessment of conducting a non-interventional post- authorization safety study (NI-PASS) of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from available secondary use data sources to replicate the Transplant Pregnancy Registry International (TPRI) study

Purpose of the assessment:

This will be a non-interventional multi-country feasibility assessment using longitudinal secondary data from large data sources in Finland, Norway, Sweden, the United Kingdom (UK), Denmark and France to assess exposure to tacrolimus and alternative immunosuppressants before conception and during pregnancy among transplant recipients, considering both maternal and paternal exposure. With pregnancy as the unit of analysis, the results will be counts of pregnancies with maternal and paternal exposure to tacrolimus and alternative immunosuppressants, considering the inclusion and exclusion criteria. The index date for each pregnancy will be defined as the date of conception and will determine the start of the observation period for each individual report of pregnancy.

Annex 4 - Specific adverse event follow-up forms

Data-lock point for this annex	31 Dec 2019
Version when annex last updated	Version 3.1

Follow-up Questionnaire for Systemic Tacrolimus Medication Errors

Email to:		**Case Number**	
Fax to:		**Patient Details:**	Age/Age group ☐ Male ☐ Female

Instructions

With this questionnaire, we would like to request specific follow-up information regarding the prescribing, dispensing, or administering of an incorrect dose of the systemic Tacrolimus formulation or medication error involving a switch between different formulations of systemic Tacrolimus. If more than one medication error occurred, complete a separate form for each medication error. Provide as much new information as possible, focusing on the information that has not previously been provided and that is relevant to the error. Consider the applicable data privacy restrictions in your country while completing this form. For cases not originating from clinical studies, attach any relevant anonymized supporting documentation, if available.

Thank you in advance for your cooperation.

Follow-up Questionnaire for Systemic Tacrolimus Medication Errors

Case Number:

SOURCE OF ERROR	PRESCRIPTION ERROR	DISPENSING ERROR	ADMINISTRATION ERROR	INTERCEPTED ERROR[1]	SWITCHING ERROR[2]
Formulation Error	☐	☐	☐	☐	☐
Dosage Error	☐	☐	☐	☐	☐
Reason for the error:					

[1] Intercepted error: Error occurred but did not reach the patient. [2] Switching error: Inadvertent or non-supervised changing from one formulation/dosage to another.

DETAILS OF ERROR

Description of the error:

How was the error recognized?

Provide additional information regarding the error:

	DRUG NAME [A]	ACTUAL DOSE (MG) / FREQUENCY	START DATE DD-MMM-YYYY	STOP DATE DD-MMM-YYYY	**BATCH/LOT #/ EXPIRY DATE** dd-Mmm-yyyy
What should the patient have received?				☐ Ongoing	
What did the patient receive?				☐ Ongoing	

[A] Brand Name – **[1]**-ADVAGRAF **[2]**-ASTAGRAF XL **[3]**-GRACEPTOR **[4]**-PROGRAF XL **[5]**-PROGRAF **[6]**-MODIGRAF (granules) **[7]**-PROGRAFT **[8]**-Generic Tacrolimus (non-Astellas)

PROVIDE SERUM TROUGH LEVELS OF TACROLIMUS BEFORE AND AFTER MEDICATION ERROR OBSERVED	BEFORE		AFTER	
	DATE dd-Mmm-yyyy	RESULT/UNIT	DATE dd-Mmm-yyyy	RESULT/UNIT
Tacrolimus serum trough levels				

ACTION TAKEN

Was the error corrected?	☐ Yes	If yes, how was the error corrected?
	☐ No	If no, why was it not corrected?

SYSTEMIC TACROLIMUS INDICATION

Indication: ☐ Liver Transplant ☐ Kidney Transplant ☐ Heart Transplant ☐ Other (please describe):

Follow-up Questionnaire for Systemic Tacrolimus Medication Errors

Case Number:

ADVERSE EVENT (AE) List any adverse events that are associated with the medication error	**START DATE** dd-Mmm-yyyy	**STOP DATE** dd-Mmm-yyyy	**SERIOUSNESS[1]**	**RELATIONSHIP TO ASTELLAS SUSPECT DRUG[2]**	**RELATIONSHIP TO MEDICATION ERROR[3]**	**OUTCOME[4]**
		☐ Ongoing				

Additional details about the adverse event(s):

[1]SERIOUSNESS CRITERIA: *1. Death*, 2. Requires/Prolongs Hospitalization, 3. Congenital Anomaly, 4. Life Threatening, 5. Persistent or Significant Disability, 6. Would have led to one of the above if left untreated (Medically Important), 7. Non-serious*

[2]RELATIONSHIP TO ASTELLAS SUSPECT DRUG: Do you consider that there is a reasonable possibility that the event may have been caused by the Astellas suspect drug? *1. Yes, 2. No*

[3]RELATIONSHIP TO MEDICAL ERROR: Do you consider that there is a reasonable possibility that the event may have been caused by the medicaton error? *1. Yes, 2. No*

[4]OUTCOME: *1. Fatal*, 2. Not recovered/Not resolved, 3. Recovered/Resolved, 4. Recovered/Resolved with sequelae, 5. Recovering/Resolving, 6. Unknown*

*FOR FATAL ADVERSE EVENT:	Autopsy ☐ Yes ☐ No ☐ Unknown	Date of Death dd-Mmm-yyyy	Autopsy Details:

OTHER RELEVANT INFORMATION

REPORTER CONTACT INFORMATION

DATE OF THIS REPORT (dd-Mmm-yyyy)	**SPECIFY AFFILIATION/FUNCTION**
	☐ Physician ☐ Pharmacist ☐ Member of the transplant team ☐ Community-based health professional ☐ Other:

NAME	**ADDRESS**	**TELEPHONE /FAX**	**EMAIL**

MEDICALLY QUALIFIED INVESTIGATOR/SUB-INVESTIGATOR FOR ASTELLAS SPONSORED STUDIES

SIGNATURE (to confirm the accuracy of the data)	**NAME**	**DATE** (dd-Mmm-yyyy)

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Data-lock point for this annex	31 Dec 2019
Version when annex last updated	Version 3.0

Not applicable.