12 October 2017
EMA/829470/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tacforius

International non-proprietary name: tacrolimus

Procedure No. EMEA/H/C/004435/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ACR	acute cellular reaction
AEs	adverse events
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve
AUC24	24-hour area under the curve
AUCinf	area under the curve from time 0 to infinity
AUC0-t	area under the curve for a dosing interval
AUC0-tau,ss	area under the curve for a dosing interval at steady state
AUClast	area under the curve from time of dosing to time of last measurable concentration
BC	British Columbia
BE	Bioequivalence
BE-GL	Bioequivalence-Guideline
BLQ:	Below Limit of Quantitation
bid	twice-daily
BMI	body mass index
BP	blood pressure
Bpm	Beats per Minute
Cavg:	average concentration: AUCtau/tau
CEP	Certificate of Suitability of the Ph.Eur.
Cmax	maximum blood concentration
Cmax,ss	maximum blood concentration at steady state
Cmin	minimum blood concentration
Ctau,ss	measured concentration at the end of the dosing interval at steady state
Ctrough	measured concentration at the end of the dosing interval
Cpd:	Pre-dose (morning) measured analyte concentrations on Days 8, 9, and 10.
C/D	concentration/dose
CI	Confidence Interval

CK	Creatine Phosphokinase
Cl^-	Chloride
CL/F	oral clearance
CrCl	creatinine clearance
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CRF	Case Report Form
CS	Clinically Significant
CsA	cyclosporine
CV	Coefficient of Variation
CYP3A	cytochrome P450 3A
DNA	desoxyribonucleic acid
DSC	differential scanning calorimetry
EASL	European Association for the Study of the Liver
EAU	European Association of Urology
EBV-PTLD	epstein-barr virus-associated posttransplant lymphoproliferative disorder
EC-MPS	enteric-coated mycophenolate sodium
eCrCl	estimated creatinine clearance
EMA	European Medicines Agency
Fb	free fraction in blood
FDA	Food and Drug Administration
fP	free fraction in plasma
FKBPI2	FK 506 binding protein-12
G	Gram
GC	Gas Chromatography
GFR	glomerular filtration rate
GMD	glucose metabolism disorder
HbA1c	haemoglobin A1c
HBsAg	Hepatitis B Surface Antigen
HCG	Human Chorionic Gonadotropin
HIV	human immunodeficiency virus

HPLC	High Performance Liquid Chromatography
ICF	Inform Consent Form
ICH	International Conference on Harmonisation
IL-2	interleukin 2
IPCs	in-process controls
IR	Infrared
IRB	Institutional Review Board
KDIGO	Kidney Disease: Improving Global Outcomes
Max	Maximum
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
ME	microemulsion
Mg=µg	Microgram
Mg=mg	Milligram
Min	Minute/Minimum
MMF	mycophenolate mofetil
mL	Milliliter
MPA	mycophenolate acid
MR	modified-release
MS	Mass Spectrometry
MSE	Mean Square Error
ms or msec	Millisecond
n	Number
NADPH	nicotinamide adenine dinucleotide phosphate
N/AP or NA	Not Applicable
N/AV	Not Available
NC	Not Calculated
NCS	Not Clinically Significant
Ng	Nanogram
NK	Not known

n.s.	not significant
NF-AT	nuclear factor of activated T cells
NMR	Nuclear Magnetic Resonance
NNRTI	nonnucleoside reverse transcriptase inhibitors
NRTI	nucleoside reverse transcriptase inhibitors
OOS	of out-of-specification
OTC	over-the-counter
Ph. Eur.	European Pharmacopoeia
PI	protease inhibitor
PK	pharmacokinetic
p.o.	Per os
PR	Prolonged-Release
PRCA	pure red cell aplasia
PRES	posterior reversible encephalopathy syndrome
PT	Preferred Term
PTLD	posttransplant lymphoproliferative disorder
PVC	polyvinyl chloride
PVDC	polyvinylidene chloride
QA	Quality Assurance
QC	Quality Control
QRS	Complex between Q and S Wave
QT	Time between Q and T Wave
QTc	QT Interval Corrected for Heart Rate
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
RH	relative humidity
SAE	serious adverse events
SD	standard deviation
SLS	Sodium Lauryl Sulfate
SmPC	Summary of Product Characteristics
SOC	System Organ Class

SOP	Standard Operating Procedures
SPK	simultaneous pancreas-kidney
SS	steady state
TLC	Thin layer chromatography
tmax	time to maximum blood concentration
t1/2	elimination half life
TBC	To be controlled
TEAEs	treatment-emergent adverse events
TGA	Thermo-Gravimetric Analysis
TSE	Transmissible Spongiform Encephalopathy
UHPLC	Ultra High Performance Liquid Chromatography
ULN	Upper Limit of Normal
ULQ	Upper Limit of Quantitation
WBC	White Blood Cell
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva B.V. submitted on 6 December 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Tacforius, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 01 April 2016.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference medicinal product, as defined in Article 10(2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

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.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Advagraf instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Prograf 0.5mg, 1mg, 3mg Capsule, hard
- Marketing authorisation holder: Astellas Pharma Europe B.V.
- Date of authorisation: 03-06-1998
- Marketing authorisation granted by:
  - Member State (EEA) - Germany
    - Community Marketing authorisation number: 41954.00.00, 41954.01.00, 41954.02.00

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Advagraf, 0.5mg, 1 mg, 3 mg, 5 mg, Prolonged-release capsule, hard
- Marketing authorisation holder: Astellas Pharma Europe B.V.
- Date of authorisation: 25-04-2007
- Marketing authorisation granted by:
  - Community

- Community Marketing authorisation number: EU/1/07/387/01-026

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Advagraf5 mg, Prolonged-release capsule, hard
- Marketing authorisation holder: Astellas Pharma Europe B.V.
- Date of authorisation: 25-04-2007
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/07/387/007, EU/1/07/387/008, EU/1/07/387/010, EU/1/07/387/24-026
- Bioavailability study number(s): TVY-P8-763, TVY-P7-885, 2016-4130

Information on paediatric requirements

Not applicable

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was :

Rapporteur: Milena Stain

- The application was received by the EMA on 6 December 2016.
- The procedure started on 23 December 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 March 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 24 March 2017.
- During the meeting on 21 April 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 May 2017.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 26 June 2017.
- During the PRAC meeting on 6 July 2017, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 20 July 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.

- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 12 September 2017.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 27 September 2017.
- During the meeting on 12 October 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Tacforius.

2. Scientific discussion

2.1. Introduction

This is a generic application for Tacforius prolonged-release hard capsules containing tacrolimus as active substance. In order to support this application the applicant conducted three bioequivalence studies in healthy volunteers:

- Single Dose 2-Stage Futility Crossover Comparative Bioavailability Study of Tacrolimus 5mg Prolonged-Release Capsules in Healthy Male and Female Volunteers / Fasting State (Protocol No:TVY-P7-885)
- Single Dose 2-Stage Futility Crossover Comparative Bioavailability Study of Tacrolimus 5 mg Prolonged-Release Capsules in Healthy Male and Female Volunteers/Fed State (Protocol No: TVY-P8-763)
- A Multiple-Dose, Comparative Bioavailability Study of Two Formulations of Tacrolimus 5 mg Prolonged Release Capsules under Fasting Conditions (Study No: 2016-4130)

The indications sought for Tacforius are the same as those of the reference medicinal product:

- 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.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard gelatin capsules containing 0.5 mg, 1 mg, 3 mg or 5 mg of tacrolimus (as monohydrate) as the active substance.

Other ingredients of the capsule content are ethylcellulose, hypromellose 2910, lactose monohydrate and magnesium stearate. The capsule shells used in 0.5 mg, 1 mg, 3 mg strengths are composed of red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171) and gelatin. The capsule shells used in 5 mg strength contain, in addition, black iron oxide (E172) and Ponceau 4R (E124). The printing ink comprises shellac, propylene glycol, black iron oxide (E172) and potassium hydroxide.

The product is available in transparent PVC/PVDC aluminium blisters or perforated unit-dose blisters wrapped in an aluminium pouch with a desiccant as described in section 6.5 of the SmPC.

2.2.2. Active substance

The chemical name of tacrolimus is [3*S*-[3*R**[E(1*S**,3*S**,4*S**)]4*S**,5*R**,8*S**,9*E*,12*R**,14*R**,15*S**,16*R**, 18*S**,19*S**,26a*R**]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxy cyclohexyl)-1-methylethenyl]-14,16-dimethoxy- 4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3*H*-pyrido[2,1-c] [1,4] oxaazacyclotricosine-1,7,20,21(4*H*,23*H*)-tetrone, monohydrate corresponding to the molecular formula $C_{44}H_{69}NO_{12}\cdot H_2O$. It has a relative molecular mass 822.05 g/mol and the following structure:

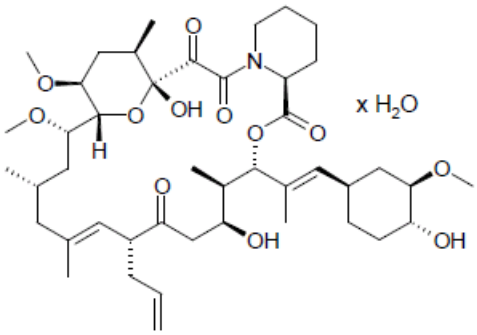

Figure 1. Structure of tacrolimus

The structure of the active substance was elucidated by a combination of elemental analysis, infrared spectroscopy (IR), NMR, mass spectrometry (MS), UV spectroscopy, differential scanning calorimetry (DSC), X-ray diffraction analysis (XRPD), chromatography (HPLC) and thermogravimetic analysis (TGA). Tacrolimus is sufficiently characterised and its structure is adequately elucidated.

Tacrolimus appears as a white to off-white non-hygroscopic powder. It is very soluble in acetone and ethanol and practically insoluble in water. Its pKa value was found to be 9.96 ± 0.70.

The structure of tacrolimus contains 14 chiral centres and 2 double bonds. Due to the biosynthetic origin, the chirality is assured by the biosynthesis and was proved by X-ray crystal structure determination. Only two epimeric products have been described in the literature so far and both were presented as potential impurities: tautomer II (tacrolimus 19-epimer) and 21-epi-tacrolimus (tacrolimus 8-epimer). No other epimeric impurities were identified during the development of the process for the manufacture of tacrolimus.

Tacrolimus is known to exist in isomorphic anhydrous form and hydrate. The active substance manufacturer consistently produces the same crystalline form, which according to the provided data is stable.

Manufacture

Detailed information on the manufacturing of the active substance was provided in the restricted part of the ASMF and was considered satisfactory.

Tacrolimus is a natural product manufactured by isolation from fermentation broth. The process consists of the following steps: inoculation and fermentation, isolation of crude tacrolimus and purification of crude tacrolimus.

Critical and non-critical process steps and parameters have been identified, the in-process controls (IPCs) applied during the synthesis of the active substance are adequate. IPCs and actions in case of out-of-

specification (OOS) for any of the intermediate products of the final active substance are outlined. Adequate specifications were presented for the different intermediates of the manufacture of the active substance. The analytical methods were sufficiently described.

The control strategy ensures consistent quality of the active substance. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances. Tacrolimus is a natural product isolated from the fermentation broth and thus the potential impurities are its analogues and isomers which are also present in the broth. Some other impurities can be degradation products, formed during the isolation. Information on the fate of potential degradation products was given.

The whole manufacturing process was designed to eliminate these potential impurities and produce pure tacrolimus. The potential impurities are controlled in the active substance by validated test methods. It has been demonstrated that the impurities are adequately controlled during manufacturing of the active substance. Tacrolimus is a fermentation product without any further synthetic modification and so it is out of scope of ICH M7.

The absence of microbiological impurities was demonstrated on three batches of tacrolimus crude intermediate.

In addition, microbial quality was determined in five consecutive recently manufactured tacrolimus bathes using Ph. Eur. method (5.1.4) and USP method <1111>. Results from three consecutive production scale batches of tacrolimus crude intermediate demonstrated absence of microbiological impurities.

The primary packaging material is of food grade and complies with the requirements of Ph. Eur. and European Directive 10/2011 as amended.

Specification

The specification for tacrolimus includes appropriate tests and limits for appearance (visual), identification (IR, HPLC), water content (Karl-Fischer), sulphated ash (Ph. Eur.), related substances (HPLC), assay including tautomer content (HPLC), residual solvents (GC) and microbiological quality (Ph. Eur.).

The proposed tests and acceptance criteria for tacrolimus are considered acceptable and justified.

The set limits for impurities are justified in accordance with the Ph.Eur. Tacrolimus monograph published in Ph.Eur. Supplement 9.3.

Limits for residual solvents have been adequately justified and are acceptable.

Optical rotation is not considered a sensitive enough test to identify stereomeric impurities. The overall stereochemistry is controlled by the fermentation organism and relevant diastereomers can be detected by the HPLC method. Therefore, a test for optical rotation is not deemed necessary.

Adequate data which shows that the polymorphic form is stable has been provided. Therefore, no test for polymorphic form is included in the specification.

The analytical procedures used in the control of the active substance have generally been satisfactorily described and validated in accordance with the ICH guidelines. Information regarding the reference standards used in the analytical testing is satisfactory.

Batch analysis data from three production scale batches of the active substance were provided. The results were within the specifications and confirm consistency of the manufacturing process from batch to batch.

Stability

Stability data from six production scale batches of active substance stored in the intended commercial packaging for up to 60 months under long term conditions (25 °C / 60 % RH) and for up to 6 months under accelerated conditions (40 °C / 75 % RH) were provided according to the ICH guidelines.

Samples were tested for appearance, water content, tautomer content, assay and related substances. The test methods were the same as for release and are stability indicating. No significant changes to any of the measured parameters were observed under long term and accelerated conditions and all remained within specification.

Photostability testing on one production scale batch following the ICH guideline Q1B was provided. Tacrolimus can be considered slightly photosensitive and for long term storage, it is recommended to be protected from light.

Stress testing on one production scale batch (heat stress in solid state and in solution, acid and alkaline stress, oxidation, UV stress in solid state and in solution) was also performed, the stability indicating nature of the analytical test method is considered acceptable.

Overall the stability results justify the proposed retest period and storage conditions.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as prolonged-release, hard gelatin capsules containing 0.5 mg, 1 mg, 3 mg, or 5 mg of tacrolimus. The capsules appear as follows:

0.5 mg: size 5 hard gelatine capsules filled with white to off-white powder; body: light orange with “0.5 mg” radial black imprinting; cap: light yellow with “TR” radial black imprinting.

1 mg: size 4 hard gelatine capsules filled with white to off-white powder; body: light orange with “1 mg” radial black imprinting; cap: white with “TR” radial black imprinting.

3 mg: size 1 hard gelatine capsules filled with white to off-white powder; body: light orange with “3 mg” radial black imprinting; cap: light orange with “TR” radial black imprinting.

5 mg: size 0 hard gelatine capsules filled with white to off-white powder; body: light orange with “5 mg” radial black imprinting; cap: greyish red with “TR” radial black imprinting.

The aim of the pharmaceutical development was to obtain generic prolonged-release capsules bioequivalent to the reference medicinal product on the EU market, Advagraf 0.5 mg, 1 mg, 3 mg and 5 mg prolonged-release hard capsules.

Key physicochemical characteristics of the active substance were discussed. Based on the presented information it can be concluded that the finished product manufacturing process and finished product storage have no impact on chiral assay and stereoisomeric impurities profile of the product.

The formulation was based on the composition of the reference product. Dissolution and bioequivalence studies served as tools in devising a suitable formulation. A formulation strategy was developed in order to optimise the manufacturing process.

The excipients of the capsule content are the same as in the reference product. Their suitability for the intended use in the specific type of product and active substance can thus be assumed. Excipient characteristics that could influence finished product quality have been adequately discussed. The formulation of the capsule content is also qualitatively the same as the reference product. Ethylcellulose is used as a prolonged release matrix former, hypromellose and lactose monohydrate function as pore formers in the ethylcellulose matrix and as dissolution enhancers.The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

In the first set of development experiments the objective was to investigate the effect of different excipient grades and quantities on product characteristics along with processability and test different capsules *in vivo* for bioequivalence. In the next set of experiments, the aim was to improve the active substance release rate and achieve bioequivalence of the product versus the reference medicinal product taking the available pilot *in vivo* results into consideration. Literature data were also considered. Further development work was focusing on 3 main areas: optimising the amount of different excipients, investigating the effect of particle size of the granules, and investigating the effect of process parameters on product characteristics. Next, the critical process parameters were investigated. Bioequivalence study results supported the conclusions from the above experiments. The tested batch was proven to be bioequivalent with the reference product. Subsequently, scale up and process optimization work was initiated.

Based on the development work, batches were manufactured for biostudy, stability and registration purposes. The manufacturing process for the pilot batches encompasses solid dispersion manufacturing, blending and encapsulation. The process used for the pilot batches gives sufficient control over the final product. The formulation and process will ensure that the physical and chemical characteristics of commercial batches of capsules will comply with the specification requirements.

Detailed information was provided on dissolution method development. Since dissolution is an important control test for a prolonged release product, two separate methods (QC1 and QC2) are used and to control unintended rapid release (“dose dumping”) and complete release respectively. Considering the data provided and taking into consideration that a similar approach for dissolution testing is used for the reference product, the chosen approach is considered acceptable. The dissolution testing conditions (apparatus, media volume and stirring speed) are in-line with the Ph. Eur. recommendations on dissolution testing. The chosen sampling time points are acceptable based on the reference product results.

The discriminatory power of the QC1 dissolution method has been sufficiently demonstrated. It was not considered necessary to demonstrate that method QC2 is discriminatory too, because any differences in the release profile would be more likely to be detected by method QC1.

Additionally the effect of alcohol on active substance release at pH 1.2 with 0%, 5%, 10%, 20% and 40% alcohol (sampling time up to 2 hours) was evaluated. Tacforius follows a similar release mechanism in the presence of alcohol as the reference product in the 5-40% concentration range, with drug release rate increasing as a function of alcohol content. Therefore, it is recommended that alcohol is not consumed by patients taking tacrolimus.

A bioequivalence study was conducted comparing test and reference products at the highest strength 5 mg. Comparative dissolution data were provided between the test and reference products batches used in the bioequivalence study showing similar profiles. A biowaiver was requested for the other lower strengths. Dissolution studies were performed in 3 different pH media 1.2, 4.5, 6.8 plus with the QC method in order to support the strength biowaiver. Dissolution profiles of the additional strengths at different pH media were

compared to the 5 mg batch biobatch and shown to be similar thus supporting the biowaiver for all three lower strengths.

The finished product is packed into transparent PVC/PVDC-aluminium blisters. PVC/PVDC-aluminium blisters are packed into a multilayer aluminium pouch with desiccant. The blister material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process of tacrolimus 0.5, 1, 3 and 5 mg prolonged-release capsules is divided into 2 phases and each phase comprises 6 main steps. Preparation of the intra-granular phase comprises paste preparation, film casting, drying, milling and sieving, base granule blending and dispensing the finished base granule. Preparation of the finished product comprises a series of blending steps to combine the granules with extra-granular excipients, encapsulation and packaging.

Critical steps have been adequately described; the in-process controls are considered appropriate and adequate.

Process validation results have been provided for three consecutive batches of each strength. According to the provided process validation reports, the maximum commercial batch sizes for which the process is validated have been defined.

Holding times proposed for the proposed intermediates were based on relevant stability studies and are found acceptable.

In conclusion, it has been demonstrated that the manufacturing process is sufficiently robust to provide assurance that hard capsules of consistent quality, complying with the designated specification, are produced.

Product specification

The finished product release and shelf-life specifications include appropriate tests and limits for description (visual), identification (UHPLC, TLC), uniformity of dosage units by content uniformity (Ph. Eur., UHPLC), dissolution (Ph. Eur., HPLC), assay (UHPLC), impurities/degradation products (HPLC), and microbiological quality (Ph. Eur.).

The specifications comply with the requirements of the Ph. Eur. for capsules as well as the ICH Q6A guideline. Detailed justification is provided on the proposed limits for known impurities and for not testing solvents or elemental impurities. The finished product is not in the scope of ICH Q3B. However, release and shelf-life limits for impurities are set based on the thresholds referenced in ICH Q3B and actual batch data. In the absence of other guidance applicable to the present finished product, the applicant´s approach for setting impurity limits is considered reasonable. The release and shelf-life limits for total impurities are acceptable.

The proposed limits for dissolution testing are set in compliance with Ph. Eur. recommendations on dissolution testing of prolonged release dosage forms (Ph. Eur.). The specified acceptable ranges are justified in compliance with the guideline on quality of oral modified release products. A test for disintegration was not included in the finished product specifications. However, this is acceptable as a dissolution test is performed. The proposed limits for microbiological quality comply with Ph. Eur.

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data from three production scale and three pilot scale batches of each strength have been presented. All data is within specification. The results show that the finished product can be manufactured with consistent quality and meet its specifications.

Stability of the product

Stability data was provided from three production scale batches of each strength stored under long term conditions for up to 18 months (25 °C / 60% RH) for the 3 and 5 mg strengths and for up to 12 months for the 0.5 and 1 mg strength. For all strengths, 6 months' stability data under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines was provided. The bracketing approach applied for different pack sizes, based on the relation of the amount of silica gel desiccant in the pouch and pack size is generally acceptable. The stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. The following parameters were investigated: description, dissolution, assay, impurities/degradation products. The methods used were the same as for release testing and are stability indicating. Under both long term and accelerated conditions, there was no change in the appearance of the capsules. Some variability within the assay and dissolution results was seen, however, no significant trend was apparent and all the results met the specifications. The known impurities increased but all results remained well below the specification limits.

In-use stability studies have been initiated in accordance with the Note for Guidance on In-use Stability Testing of Human Medicinal Products (CPMP/QWP/2934/99). Blisters in the opened aluminium pouch and blisters kept outside the aluminium pouch were tested under long term storage conditions. No change in the appearance of the capsules was observed. There was some variability within the assay and dissolution results, however, no significant trend was apparent and the results always met the specifications. There was some increase in known impurity levels, however all results were well within the acceptance criteria. Tacrolimus prolonged-release capsules, packaged in PVC/PVDC–Aluminium blisters are stable for at least 12 months after first opening the aluminium pouch. In-use stability of the finished product should also be confirmed with a batch close to the end of its shelf-life. In this regard the CHMP recommended the MAH to perform a 100 day in-use stability of the finished product using the 100 capsule pack with a batch close to the end of the shelf-life. Taking into account that the finished product is a "non-critical" dosage form (capsule, oral use) and also the provided capsules bulk stability data this is considered acceptable.

Photostability testing was performed on one commercial scale batch of the highest and lowest strengths according to ICH Q1B. The applied bracketing of strengths is acceptable. The appearance of the unprotected exposed capsules did not change. There was some decrease in assay in exposed unprotected samples, which was more pronounced in case of the 0.5 mg strength. However, all results were within the specification limits. Impurity levels generally increased after exposure and, for certain unknown impurities, were above the specification limit. Exposed samples of the product packed in blister and aluminium pouch were not affected. The results show that the finished product is sensitive to light and that the selected packaging materials are capable of providing proper protection from its effect.

A forced degradation study was carried out on the finished product in order to demonstrate the stability indicating nature of the assay and related substances methods. Samples of finished product were tested after

exposure to acidic, basic, oxidative conditions, elevated temperature, and UV light. The results of degradation studies demonstrate that that the assay and related substances methods are stability indicating.

Based on the provided stability data, the proposed shelf life of 30 months for the 3 mg and 5 mg strength capsules and 2 years for the 0.5 mg and 1 mg capsules, as stated in the SmPC (section 6.3) is acceptable. The product must be stored in the original package in order to protect from light and moisture but does not require any special temperature storage conditions as stated in the SmPC (section 6.4).

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Gelatin used in the hard capsules is obtained from bovine sources. Valid TSE CEPs from the suppliers of the gelatin were provided.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there was a minor unresolved quality issue regarding the in-use stability of the finished product (refer to “Stability of the product” above and “Recommendation for future quality development” below) having no impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- In-use stability of the finished product should be confirmed with a batch close to the end of the shelf-life. In this regard the applicant committed to perform a 100 day in-use stability study of the finished product using the 100 capsule pack with a batch of the tested strengths close to the end of its shelf-life.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable. Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment (ERA) data were submitted. This was justified by the applicant as the introduction of Tacrolimus manufactured by Teva B.V. is considered unlikely to result in any significant increase in the combined sales volumes for all tacrolimus containing products and the exposure of the environment to the active substance. The CHMP agreed with this justification.

2.3.3. Discussion on non-clinical aspects

The non-clinical overview on the pharmacology, pharmacokinetics and toxicology justifies based on up-to-date and adequate scientific literature why there is no need to generate additional non-clinical data. This was considered acceptable and it was agreed that no further non-clinical studies were required. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile was discussed and was considered acceptable.

The Applicant's justification for omission of an environmental risk assessment was considered acceptable.

2.3.4. Conclusion on the non-clinical aspects

The CHMP concluded that there were no objections to granting the approval of Tacforius 0.5 mg, 1 mg, 3 mg, 5 mg prolonged-release hard capsules from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for prolonged release hard capsule, containing tacrolimus. To support the marketing authorisation application the applicant conducted 3 bioequivalence studies, 2 with cross-over design and one comparative bioavailability study of two formulations of Tacrolimus 5mg prolonged release capsules. These studies were the pivotal studies to support the efficacy and safety of the applied medicinal product.

GCP

The bioequivalence studies were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

Biowaiver for additional strengths

The applicant applied for the marketing authorization for four different strengths of tacrolimus prolonged release hard capsules- 0.5 mg, 1 mg, 3 mg and 5 mg. According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98), the bioequivalence was demonstrated at the highest strength (i.e. 5 mg). The bioequivalence for the other strengths was asked to be waived based on the following general requirements:

1. Linearity

   According to the Advagraf EPAR (Scientific discussion 2007), linearity was demonstrated in the dose range of 1.5 mg to 10 mg. At the time of the submission, no information regarding linearity in lower dose ranges was provided. The applicant was asked to present further information concerning dose linearity and provided information showing linearity for the 1 mg strength but failed to do so for the 0.5 mg strength.

   CHMP asked the applicant to provide additional information supporting dose linearity also for the 0.5 mg strength.

   Although no direct pharmacokinetic data for the 0.5 mg strength was available, the applicant presented relevant published literature and in-house data, discussing it in sufficient detail. The discussion provides information to expect linear pharmacokinetics over the whole dose range (0.5 mg – 10 mg) of tacrolimus and a biowaiver for the lowest strength (0.5 mg) was hence accepted.

2. General biowaiver criteria:

   - The applicant assured that the pharmaceutical products submitted in this application are manufactured by the same manufacturing process at the proposed commercial manufacturing site.
   - All strengths had the same qualitative composition, except the colouring agents. The different colours of the gelatine are deemed acceptable for discriminations reasons.
   - Referring to proportionality of compositions, it is regarded fulfilled for the capsule filling, but it is not seen with the gelatin capsule and the colour agents. As Tacforius is a prolonged release product, according to the guideline there is a deviation in this condition. But since the sub-condition “the amount of the active substance is less than 5 % of the tablet core weight, the weight of the capsule content” is fulfilled (it is in all strengths below 1%), the quantitatively proportional composition of the strengths can be regarded fulfilled. Furthermore, the different gelatine content is related to the different standardised capsule sizes.

- Dissolution studies were performed in 3 different pH media (1.2, 4.5 and 6.8) in order to confirm the adequacy of waiving additional in vivo bioequivalence testing referring to the 4 different strengths of Tacforius.

  In addition, dissolution studies in the media intended for drug product release were also performed.

  The dissolution profiles of the different strengths were considered as similar.

Effect of alcohol on the active substance release

According to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1), in vitro dissolution tests were performed to check the compatibility of the proportional prolonged release formulation of TEVA finished products with alcohol on the Tacforius 0.5 mg and 5 mg PR Capsules and to compare the 0.5 mg and 5 mg EU reference product Advagraf.

Dissolution conditions used for the alcoholic compatibility study were the same as in the NaCl, HCl pH=1.2 medium, but a justified range of alcohol (i.e. 5%, 10%, 20% and 40%) was added. The alcoholic dissolution testing was performed on 12 capsules with sampling up to 2 hours.

Although not all graphs were totally similar at all time points, comparable increase can be observed in the active substance release with the increase of the alcohol content in the dissolution medium in case of Teva and reference products.

Teva prolonged release formulation follows a similar release mechanism in the presence of alcohol as the reference product in the 5-20% concentration range. In the media containing 40% alcohol, Teva products and Advagraf products exhibited an immediate-release like profile, which was even more pronounced in case of the 0.5 mg strength, where both the reference and the test products showed complete dissolution after 15 minutes.

Both the reference and Teva products are clearly incompatible with 40% ethanol. But the 40% ethanol concentration can hardly be reached in the stomach in vivo and is hence physiologically not regarded as relevant. Furthermore, it does not seem likely that a patient with kidney or liver transplantation will consume tacrolimus capsules together with high amounts of high percentage alcohol.

Clinical studies

To support this application, the applicant has submitted three bioequivalence studies.

The chosen studies are in line with the recommendation of the EMA Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96Corr1), generally required for demonstrating bioequivalence between prolonged released formulations for oral administration in:

- a single-dose fasting study comparing test and reference drug product
- a single-dose fed study using a high-fat meal comparing test and reference drug product
- a multiple-dose study comparing test and reference drug product.

Table 1. Tabular overview of clinical studies

Dimension	Conditions	Study Number	Test Product	Test Product Batch Number	Test Product Batch Size
Pivotal	Fed	**TVY-P8-763**	Tacrolimus 5 mg Prolonged-Release Capsules	1731015	100,000
Pivotal	Fasting	**TVY-P7-885**	Tacrolimus 5 mg Prolonged-Release Capsules	1731015	100,000
Pivotal	Fasting	**2016-4130**	Tacrolimus 5 mg Prolonged-Release Capsules	1731015	100,000

As stated above (see heading Exemption), the bioequivalence was stablished at only one strength (5 mg prolonged release capsules) and it was claimed a waiver to the lower strengths as the following general requirements were met:

1) Linearity in pharmacokinetics was given
2) General biowaiver criteria were fulfilled
3) Results of in vitro dissolution tests (complementary to bioequivalence studies) at three different buffers (normally pH 1.2, 4.5 and 6.8) and the media intended for drug product release (QC media), obtained with the batches of test and reference products that were used in the bioequivalence study were reported accordingly.
4) Referring to the modified release guideline (PK and clinical), the substance should comply with a multiple unit formulation. Since the composition was proportional, the formulation contained identical base granules (containing the release controlling excipients, produced by the same manufacturing process) and the dissolution profiles were in principle regarded as similar (based on a bootstrap similarity factor calculation), therefore the prerequisite was fulfilled for a multiple unit formulation.

Dissolution tests complementary to BE studies

The dissolution profiles of the Teva and reference products used in pilot bioequivalence studies were tested throughout the physiological pH range for 24 hours. The data obtained demonstrated that the use of surfactant was warranted. According to the EMA Guideline on quality of oral modified release products (EMA/492713/2013), in principle surfactant could be used in the dissolution medium, the amount needed should be justified. To increase the solubility of tacrolimus a surfactant was used and its level was justified. Sink conditions were not reached, but total dissolution could be reached with this surfactant.

Only small differences were present in the otherwise similarly shaped graphs between the different biobatches of Advagraf and Tacforius 5 mg prolonged release capsules in the different media. Those differences were regarded as too small to be of importance for the real in vivo behaviour. Especially and

according to the BE-GL, bioequivalence of the 5 mg test and reference products could be clearly shown in the BE-studies.

For the 3 lower strengths (0.5 mg, 1mg and 3mg) a strengths-biowaiver was claimed by the applicant.

2.4.2. Pharmacokinetics

Study TVY-P8-763: Single Dose 2-Stage Futility Crossover Comparative BA Study of Tacrolimus 5 mg Prolonged-Release Capsules in Healthy Male and Female Volunteers / Fed State

Methods

Study design

The study was a single-centre, randomized, single dose, laboratory-blinded, two-period, two-sequence, two-stage, futility, crossover design in healthy male and female subjects under fed conditions to evaluate the comparative bioavailability between the test (Tacforius 5 mg prolonged-release capsule) and the reference (Advagraf 5 mg prolonged-release capsule) products.

The clinical part of the study took place from 17th of March 2016 till 6th of July 2016.

Subjects arrived at the clinical site at least 10.5 hours prior to dosing. After a supervised overnight fast, subjects received a standardized high-fat, high-calorie meal 30 minutes before drug administration. Thirty minutes after the start of breakfast, a single 5 mg oral dose of the assigned formulation was administered in the morning with approximately 240 mL of water at ambient temperature, starting at 08:00, to one subject per minute.

The 60 included subjects received a single oral dose of 5 mg of the randomly assigned drug product in each period, separated by a 14-day wash-out period.

In each study period, 25 blood samples were collected for each subject. Blood samples for pharmacokinetic measurements were collected prior (not more than 2 hrs) to drug administration and at 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.33, 4.67, 5.00, 5.50, 6.00, 7.00, 8.00, 9.00, 10.00, 12.00, 16.00, 24.00, 48.00, 72.00, 96.00, 120.00, and 144.00 hours following drug administration.

The analysed compound was the parent, what is in line with the SmPC of the reference product and with the product specific guideline on tacrolimus (EMA/CHMP/159744/2016). The analysed matrix was whole blood, what is also in line with the product specific guideline (EMA/CHMP/159744/2016) and results from tacrolimus binding strongly to erythrocytes.

The sampling period of 144 hrs, AUC_{0-144}hrs covering more than 80% of AUC_{0-inf} (residual area of 4.46 and 4.49% for test and reference, respectively) and the sampling scheme (median of 6.0 and 5.5 hrs for test and reference respectively) are regarded as adequate in relation to the relevant PK parameters.

Subjects were allowed to leave the clinical site after the 48-hour post dose blood draw and were asked to return to the clinical site before each of the 4 remaining blood samples.

The wash-out period of 14 days (336 hrs) is regarded as long enough, since it covers more than the requested at least 5 elimination half-lives.

The products were administered to 60 subjects in a 2-stage futility design: 28 subjects were dosed in the first group (stage 1), 32 subjects in the second group (stage 2).

Statistical analysis was done separately for the data of the first stage, and on the combined data of the two stages. The first analysis was performed after the first stage was completed.

Normally, interim analyses require an adjustment for multiplicity of testing. In this case, the interim analysis was only done to prematurely recognize, if the study were on the right way or if it would fail. Failure would have led to the termination of the study. Since it was predefined in the protocol, that BE would only be calculated based on both stages, this is deemed an acceptable method that does not need further adjustment than the inclusion of the stage as additional statistical factor, as it was done by the applicant.

Blinding of the subjects or the clinical staff is not regarded necessary in a bioequivalence study comparing PK parameters. Blinding of the bioanalytical staff was assured, what is deemed adequate for the evaluation of bioequivalent PK parameters.

Test and reference products

Tacforius 5 mg manufactured at the proposed commercial site has been compared to Advagraf (Tacrolimus) 5 mg by Astellas Ireland Co. Ireland. The applicant confirmed that the unit formula of the 5 mg biobatch is identical to the proposed commercial formulation.

Population studied

Study population consisted of 60 non- or ex-smoking, male (33) and female (27) volunteers, between 19 and 60 years of age, with a BMI from 18.5 to 29.6 kg/m2 who were judged healthy based on a medical history, ECG, laboratory evaluation, physical examination and vital signs measurements, willing to use an acceptable effective method of contraception. Among the patients, 51 were White, 6 Black, 2 Asian, 1 Other (white/black). A total of 60 subjects were included in this study and, after randomization, 57 subjects (95%) received the Test and 59 subjects (98%) received the Reference.

Four subjects (7%) discontinued the study, of which 2 (3%) discontinued for personal reasons and 2 (3%) were withdrawn due to positive results of urine drug screen (positive for cotinine, obviously having smoked, although prohibited). 56 subjects (93%) completed the study.

Subject 309 was excluded from the pharmacokinetic and statistical analysis after completing both periods and receiving both formulations under study due to 9 episodes of diarrhoea during period 2, from 5.87 to 16.02 hours following drug administration. Considering the long period of time over which the diarrhoea was observed (more than 2 times the expected Tmax of 4.6 hours), and the first episode started shortly after the expected Tmax, absorption could still have been occurring and be compromised. Hence, the exclusion of the PK and statistical analysis can be accepted.

Pharmacokinetic Population

55 subjects were included in the pharmacokinetic and statistical analysis.

Out of those 55, three subjects (subjects 306, 333 and 351) were included for the Cmax and Tmax parameters only, due to diarrhoeal episodes.

The inclusion of the three subjects on the AUC-results is considered to have only small influence on the total outcome. Hence bioequivalence is shown between the 5 mg Test formulation and the 5 mg Reference product.

Safety Population

The safety population included all of the subjects who entered the study and received at least one of the investigational products (n= 60).

Analytical methods

The analytical part of the study lasted from 11.04.2016 till 03.08.2016. The study samples were obtained stored at a nominal temperature of -20ºC. A total of 2898 samples from 60 subjects (25 time-points per subject, 2 periods) were analysed; the theoretical amount of samples is 3000.

As regards Tacrolimus (analyte), internal standard was Ascomycin; samples were extracted from a 1.0 mL aliquot of K2EDTA human whole blood by liquid-liquid extraction. The extracted samples were injected into a liquid chromatograph.

The detection method used was tandem mass spectrometry detector.

Quantitation was determined by peak area ratio method. A weighted (1/c2) linear regression was performed to determine the concentration of the analyte.

The validated calibration range for the assay of Tacrolimus was from 50.0 pg/mL to 50.00 ng/mL.

The analytical method for the determination of Tacrolimus in human whole blood as well as respective validation was described adequately; the validation was performed according to the requirements of the EMA "Guideline on bioanalytical method validation" (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr 2*). Acceptance criteria were in a plausible range and were fulfilled.

The bioanalytical method demonstrates acceptable performance and is suitable for the determination of Tacrolimus in K2EDTA human whole blood over the calibration range.

The bioanalytical methodology explained above was also performed in the study TVY-P7-885 and the study 2016-4130.

Pharmacokinetic variables

The following pharmacokinetic parameters were estimated using a non-compartmental approach:

AUC_{0-t} Cumulative area under the blood concentration-time curve, calculated from 0 to Time of last observed quantifiable blood concentration (T_{LQC}) using the linear trapezoidal method.

$AUC_{0-\infty}$ Area under the blood concentration-time curve extrapolated to infinity (calculated as AUC0-T + $\hat{C}LQC/\lambda z$, where $\hat{C}LQC$ is the estimated concentration at time T_{LQC})

Residual area Extrapolated area (i.e. percentage of AUC0-∞ due to extrapolation from TLQC to infinity).

$$\text{Residual area} = 100 * \frac{(AUC_{\infty} - AUC_{T})}{AUC_{\infty}}$$

C_{max}	Maximum observed blood concentration
T_{max}	Time of maximum observed blood concentration; if it occurs at more than one time point, T_{max} is defined as the first time point with this value
λz	Apparent elimination rate constant, estimated by linear regression of the terminal linear portion of the log concentration versus time curve
T_{half}	Terminal elimination half-life, calculated as ln(2)/ λz

Cmax, AUC0-t and AUC0-∞ were the main pharmacokinetic parameters of interest for the bioequivalence studies.

Other parameters such as Tmax, residual area, λ Z and Thalf were provided for information purposes only.

Due to the long Thalf (according to Advagraf SmPC approx. 43 hours, from the results of this study with fed subjects, around 33.5 hours) accumulation is for sure if taken once daily as recommended.

AUC0-t was measured till 144 hrs.

The selected pharmacokinetic parameters are in accordance with the modified-released Guideline and accepted.

Statistical methods

Descriptive statistics were calculated for blood concentrations at each individual time point and for all pharmacokinetic parameters. The individual blood concentration/time profiles were presented using the actual sampling times whereas the mean blood concentration/time profiles were presented using the theoretical sampling times. The pharmacokinetic and statistical analyses were generated using Phoenix® WinNonlin® version 6.3, Phoenix® ConnectTM version 1.3.1 and SAS® version 9.4 (GLM procedure).

The statistical analysis was based on a parametric ANOVA model of the pharmacokinetic parameters; the two-sided 90% confidence interval of the ratio of geometric means for the Cmax, AUC0-t and AUC0-∞ was based on ln-transformed data; Tmax was based on a non-parametric approach.

Test of fixed period, sequence and treatment effects were based on the Wilcoxon's rank sum test (Mann-Whitney U-test). All other un-transformed and ln-transformed pharmacokinetic parameters were statistically analysed using an Analysis of Variance (ANOVA) model. The fixed factors included in this model were to be the subject effect (nested within sequence), the treatment received, the period at which it was given, as well as the sequence in which each treatment was received. If it was decided to proceed with the second stage, the ANOVA model was to be modified to include terms for stage, sequence, treatment, subject (nested within sequence-by-stage), period (nested within stage), and the sequence-by-stage interaction when analysing the combined data from the two stages.

The formula to estimate the intra-subject coefficient of variation was to be $\sqrt{e^{MSE}-1}$, where MSE is the Mean Square Error obtained from the ANOVA model of the ln-transformed parameters.

Bioequivalence could be concluded only based on the combined data of both stages, but not considering the data from just one of the stages. Since the study could not be finished with a bioequivalence conclusion after

the first stage, there was no risk for alpha inflation for the bioequivalence assessment of the combined stages.

Statistical inference of tacrolimus was based on a bioequivalence approach using the following standards:

The ratio of geometric LSmeans with corresponding 90.00% confidence interval calculated from the exponential of the difference between the Test and Reference products for the ln-transformed parameters Cmax should have been within the 80.00 to 125.00% bioequivalence range.

The ratio of geometric LSmeans with corresponding 90.00% confidence interval calculated from the exponential of the difference between the Test and Reference products for the ln-transformed parameters AUC0-t and AUC0-∞ should all have been within the 90.00 to 111.11% bioequivalence range.

According to the Bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) and the addressed PKWP Q&A (EMA/618604/2008 Rev. 13), since tacrolimus is a narrow therapeutic index drug, a tightened acceptance interval of 90.00- 111.11% for AUC is recommended. Nevertheless, tacrolimus doesn't need narrowing of the acceptance range for the Cmax.

Results

Table 2. Pharmacokinetic parameters for tacrolimus (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic <geometric> mean	**SD CV%**	**arithmetic <geometric> mean**	**SD CV%**
AUC_{0-t}	140303.5 pg*h/mL <132404.2 pg*h/mL>	46361.0 33.0%	139832.2 pg*h/mL <131191.9 pg*h/mL>	49501.5 35.4%
$AUC_{0-\infty}$	147151.8 pg*h/mL <138651.6 pg*h/mL>	49296.0 33.5%	146633.8 pg*h/mL <137328.2 pg*h/mL>	52163.0 35.6%
C_{max}	7298.5 pg/mL <6827.6 pg/mL>	2495.5 34.2%	6860.5 <6572.8 pg/mL>	1926.4 28.1%
T_{max}*	6.00 (2.50-16.07) hrs		5.50 (1.50-16.00) hrs	

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t (=144) hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration (* median, range)

Table 3. Statistical analysis for tacrolimus (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
AUC_{0-t}	100.92	97.63-104.33%	10.1%
$AUC_{0-\infty}$	100.96	97.60-104.44%	10.3%
C_{max}	103.88	97.81-110.32%	19.0%
* estimated from the Residual Mean Squares			

As described in the table above, bioequivalence has been appropriately shown between the 5 mg Test formulation and the 5 mg Reference product when administered as a single dose under fed conditions.

Table 4. Summary of Blood Tacrolimus Pharmacokinetic Parameters

PARAMETER	TEST (n=55)*		REFERENCE (n=55)*	
	MEAN	C.V. (%)	MEAN	C.V (%)
C_{max} (pg/mL)	7298.5	(34.2)	6860.5	(28.1)
ln (C_{max})	8.8349	(4.1)	8.7938	(3.3)
T_{max} (hours)**	6.00	(2.50-16.07)	5.50	(1.50-16.00)
AUC_{0-t} (pg.h/mL)	140303.5	(33.0)	139832.2	(35.4)
ln (AUC_{0-t})	11.7959	(2.9)	11.7859	(3.1)
$AUC_{0-\infty}$ (pg.h/mL)	147151.8	(33.5)	146633.8	(35.6)
ln ($AUC_{0-\infty}$)	11.8418	(3.0)	11.8321	(3.1)
Residual area (%)	4.46	(48.4)	4.49	(45.0)
λ_z (hours $^{-1}$)	0.0215	(17.8)	0.0213	(17.8)
T_{half} (hours)	33.24	(19.0)	33.66	(19.0)

*n=52 for λ_z, AUC_{0-t}, $AUC_{0-\infty}$, Residual area, T_{half}
** Median (range)

Additionally provided parameters also support bioequivalence of Tacforius 5 mg prolonged release capsules to Advagraf 5 mg prolonged release capsules.

Protocol deviations

The main reasons for blood sampling time deviations were: Difficulty with vein/catheter, technical oversight, subject is early/late /absent (return visit), late due to previous subject sample. The mentioned reasons and number of deviations are considered to be in a normal range for clinical BE-studies done with 60 subjects (in

a cross-over design). The protocol deviations reported for the subjects included in the analysis are judged to have no significant impact on the bioequivalence assessment or on subject's safety.

Safety data

A total of 60 subjects were included in the study. After randomization, 57 subjects (95%) received the test (Tacrolimus) and 59 subjects (98%) received the reference (Advagraf). All subjects who received at least one of the investigational products (n= 60) were included in the safety population. Safety was evaluated through assessment of adverse events, standard laboratory evaluations, and vital signs, ECG findings, physical examination findings, and concomitant medication usage. A tuberculin blood or skin test was also performed (when required).

Adverse events

All AEs occurring after the initiation of the treatment were referred to as TEAEs (treatment-emergent adverse events). A total of 35 TEAEs were reported by 20 (33%) of the 60 subjects who participated in this study. Of these events, 19 occurred after administration of the test and the other 16 after administration of the reference.

The TEAEs were considered drug-related in 74% of occurrences, following the Test administration, and in 75% of occurrences, following the Reference administration. The TEAEs reported in this study were most commonly from the SOC gastrointestinal disorders (5% Test and 12% Reference). The most frequently reported TEAEs in this study were diarrhoea (5% Test and 3% Reference) and vessel puncture site bruise (5% Test and 2% Reference). Other TEAEs, reported with a lower frequency (3%) only following the administration of the reference, included dyspepsia, nausea, and back pain. The remaining TEAEs were reported by no more than 1 subject (2%) within each group.

The incidence of TEAEs was similar following the administration of the Test and the Reference (23% and 19%, respectively). Also, the incidence of drug-related TEAEs was similar following the administration of the Test and the Reference (18% and 14%, respectively). Overall, most of the TEAEs were deemed mild (31 TEAEs, 89%) or moderate (3 TEAEs, 9%) in severity.

One severe TEAE (diarrhoea) was experienced by one subject (2%) following the administration of the Test. This TEAE was deemed drug-related by the investigator and resolved approximately within 10 hours. Data from one subject were withdrawn from the PK analysis accordingly.

The majority of the TEAEs were considered resolved at the study completion. Few TEAEs were ongoing at the end of the study; however, they were considered not clinically significant by the investigator.

Two persons decided to withdraw consent due to AE (Subject 323 experiencing symptoms of moderate upper respiratory tract infection, the other subject experiencing nausea).

No SAEs and no deaths were reported in any of the subjects enrolled in this study. No subject was withdrawn by the investigator for safety reasons.

Clinical laboratory evaluation:

The main abnormal on-study laboratory values were minimal deviations of haematology values like eosinophils, Hkt, Hb, lymphocytes, MCV and platelets, as well as traces of blood and leukocytes in the urine. The judgements of "not clinically significant" are understandable from a clinician's point of view (females

being included). All serology results were negative, all serum pregnancy tests were negative and all tuberculin test results at screening were negative.

Vital signs, ECGs, physical findings

Generally, the subjects showed vital signs within normal range in both treatment groups. Slight tachycardia, and slightly elevated blood pressure values were presented and regarded as NCS what can be accepted from a clinician's point of view. No clinically significant abnormal physical examination findings were recorded in this study.

Concomitant Medications

Two subjects (3%) received concomitant medication during this study. Subject 323 received Tylenol Cold for Night (acetaminophen /dextromethorphan hydrobromide/phenylephrine hydrochloride/chlorpheniramine maleate) for the treatment of a moderate upper respiratory tract infection (URTI). Due to this infection this subject withdrew the consent. Subject 350 received acetaminophen off site on for a mild sore throat prior to dosing in period 2. The impact of the use of these medications was assessed and they were considered to have no impact on the pharmacokinetic evaluations of this study.

Study TVY-P7-885: Single Dose 2-Stage Futility Crossover Comparative BA Study of Tacrolimus 5 mg Prolonged-Release Capsules in Healthy Male and Female Volunteers / Fasting State

Methods

Study design

The study was a single-centre, randomized, single dose, laboratory-blinded, two-period, two-sequence, two-stage, futility crossover design in healthy male and female subjects under fasting conditions to evaluate the comparative bioavailability between the test (Tacforius 5 mg prolonged-release capsule) and the reference (Advagraf 5 mb prolonged-release capsule) products. The clinical part of the study took place from 3rd of March 2016 to 23rd of June 2016.

After a supervised overnight fast, a single 5 mg oral dose of the assigned formulation was administered to the study participants in the morning with approximately 240 mL of water at ambient temperature, starting at 08:30, to one subject per minute. Fasting continued for at least 4 hours following drug administration, after which a standardized lunch was served. The 100 included subjects received a single oral dose of 5 mg of the randomly assigned drug product in each period, separated by a 14-day wash-out period.

In each study period, 24 blood samples were collected for each subject. Blood samples for pharmacokinetic measurements were collected (not more than 2 hours) prior to drug administration and at 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 24.00, 48.00, 72.00, 96.00, 120.00, and 144.00 hours following drug administration.

The analysed compound was the parent, what is in line with what is mentioned in the SmPC of the reference product and with the product specific guideline on tacrolimus (EMA/CHMP/159744/2016). The analysed matrix was whole blood, what is in line with what is recommended in the product specific guideline (EMA/CHMP/159744/2016) and results from tacrolimus binding strongly to erythrocytes.

The sampling period of 144 hrs, $AUC_{0-144hrs}$ covering more than 80% of AUC_{0-inf} (residual area of 4.42 and 4.34% for test and reference, respectively) and the sampling scheme (median of 1.75 hrs for test and reference products) are regarded as adequate in relation to the relevant PK parameters.

Subjects were allowed to leave the clinical site after the 48-hour post dose blood draw and were asked to return to the clinical site before each of the 4 remaining blood samples.

The wash-out period of 14 days (336 hrs) is regarded as long enough, since it covers more than the requested at least 5 elimination half-lives. Nevertheless, one sample in period 2 had a pre-dose concentration of 57.0 pg/mL. But since this pre-dose concentration was below 5% of the corresponding Cmax, it was included in the PK and statistical analysis without adjustment, as predefined in the protocol and in line with the Bioequivalence guideline (CPMP/EWP/QWP/1401/98). Based on the long and variable half-life of tacrolimus, this single and very low pre-dose concentration is acceptable.

The products were administered to 100 subjects in a 2-stage futility design: 30 subjects were dosed in the first group (stage 1), 70 subjects in the second group (stage 2).

Statistical analysis was done separately for the data of the first stage, and on the combined data of the two stages. The first analysis was performed after the first stage was completed. The interim analysis was only done to prematurely recognize, if the study were on the right way or if it would fail. Failure would have led to the termination of the study. Since it was predefined in the protocol, that BE would only be calculated based on both stages, this is acceptable method that does not need further adjustment than the inclusion of the stage as additional statistical factor (besides treatment, period, sequence and subject), as it was done by the applicant. Blinding of the subjects or the clinical staff was not regarded necessary in a bioequivalent study comparing PK parameters. Analysts were blinded to the sequence of administration of test and reference product to the individual subjects.

Test and reference products

Refer to *Test and reference products* of the study *Study TVY-P8-763.*

Population studied

Study population consisted of 100 non- or ex-smoking, male (41) and female (57) volunteers, between 18 and 60 years of age, with a BMI from 19.35 to 29.92 kg/m2 who were judged healthy based on a medical history, ECG, laboratory evaluation, physical examination and vital signs measurements, willing to use an acceptable effective method of contraception. Among the patients, 91 were White, 3 Black, 2 Asian and 4 Other. A total of 100 subjects were included in this study and after randomization, 98 subjects (98%) received the Test and 99 subjects (99%) received the Reference. Three subjects (3%) discontinued the study, 2 for personal reasons and 1 due to difficulties with blood collection.

Pharmacokinetic Population

All 97 completers were included in the pharmacokinetic and statistical analysis.

Originally subject 033 (did not show up for the 144.00-hour blood sample in period 1) and subject 077 (diarrhoea occuring 11 hours 15 min post dose in period 1) were included for the Cmax and Tmax parameters only for period 1. The applicant provided the AUC parameters of these two subjects as well and showed that the results had only small influence on the total outcome.

Safety Population

The safety population included all of the subjects who participated in the study and received at least one of the investigational products under study (n= 100).

Analytical methods

The analytical part of the study lasted from 30.03.2016 till 26.07.2016.

4704 samples from 100 subjects (25 time-points per subject, 2 periods) were analysed, the theoretical amount of samples was 4800. For more detailed information about the analytical methods performed in this study, please refer to the study TVY-P8-763 above. The bioanalytical method demonstrates acceptable performance and is suitable for the determination of Tacrolimus in K2EDTA human plasma over the calibration range.

Pharmacokinetic variables

Please refer to the study TVY-P8-763 above.

Statistical methods

Please refer to the study TVY-P8-763 above.

Results

Table 5. Pharmacokinetic parameters for tacrolimus (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic <geometric> mean	SD CV%	arithmetic <geometric> mean	SD CV%
AUC_{0-t}	206298.9 pg*h/mL <194927.3 pg*h/mL>	70350.3 34.1%	211747.3 pg*h/mL <200696.9 pg*h/mL>	68589.1 32.4%
$AUC_{0-\infty}$	216295.4 pg*h/mL <203992.6 pg*h/mL>	74823.4 34.6%	222087.2 pg*h/mL <209843.1 pg*h/mL>	74041.5 33.3%
C_{max}	11330.4 pg/mL <10408.4 pg/mL>	5119.5 45.2%	11588.6 pg/mL <10968.6 pg/mL>	3792.8 32.7%
T_{max}*	1.75 (0.75-6.00) hrs		1.75 (0.75-5.00) hrs	

AUC_{0-t} area under the plasma concentration-time curve from time zero to t (=144) hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
T_{max} time for maximum concentration (* median, range)

Table 6. Statistical analysis for tacrolimus (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
AUC_{0-t}	97.15	93.45-100.99%	16.2%
$AUC_{0-\infty}$	97.23	93.53-101.07%	16.2%
C_{max}	94.92	89.14-101.7%	26.8%
* estimated from the Residual Mean Squares			

Table 7. Summary of Blood Tacrolimus Pharmacokinetic Parameters

PARAMETER	TEST (n=97)*		REFERENCE (n=97)*	
	MEAN	C.V. (%)	MEAN	C.V (%)
C_{max} (pg/mL)	11330.4	(45.2)	11588.6	(32.7)
ln (C_{max})	9.2504	(4.4)	9.3028	(3.7)
T_{max} (hours)**	1.75	(0.75-6.00)	1.75	(0.75-5.00)
AUC_{0-t} (pg.h/mL)	206298.9	(34.1)	211747.3	(32.4)
ln (AUC_{0-t})	12.1804	(2.8)	12.2096	(2.8)
$AUC_{0-\infty}$ (pg.h/mL)	216295.4	(34.6)	222087.2	(33.3)
ln ($AUC_{0-\infty}$)	12.2258	(2.9)	12.2541	(2.8)
Residual area (%)	4.42	(44.3)	4.34	(45.4)
λ_z (hours $^{-1}$)	0.0212	(18.3)	0.0213	(17.8)
T_{half} (hours)	33.72	(18.4)	33.61	(18.0)

* Median (range)
** n=95 for AUC_{0-t}, $AUC_{0-\infty}$, Residual area, λ_z, T_{half}

Bioequivalence has been appropriately shown between the 5 mg Test formulation and the 5 mg Reference product when administered as a single dose under fasting conditions.

Protocol deviations

The main reasons for blood sampling time deviations were: Difficulty with vein/catheter, technical oversight, subject is early/late/absent (return visit), and other reasons. The mentioned reasons and number of deviations are considered to be in a normal range for clinical bioequivalence studies done with 100 subjects (in a cross-over design).The protocol deviations reported for the subjects included in the analysis are judged to have no significant impact on the bioequivalence assessment or on subject's safety.

Safety data

A total of 100 subjects were included in this study. After randomization, 98 subjects (98%) received the Test (Tacrolimus) and 99 subjects (99%) received the reference (Advagraf). All subjects who received at least one of the investigational products (n= 100) were included in the safety population. Safety was evaluated through assessment of adverse events, standard laboratory evaluations, and vital signs, ECG findings, physical examination findings, and concomitant medication usage. A tuberculin blood or skin test was also performed (when required).

Adverse events

All AEs occurring after the initiation of the treatment were referred to as TEAEs. A total of 68 TEAEs were reported by the 33 (33%) of the 100 subjects who participated in this study. Of these TEAEs, 34 occurred following the administration of each the Test and the Reference.

The most frequently reported TEAE in this study was headache, which was experienced by 7 subjects following the administration of each the Test and the Reference.

Other TEAEs were reported with a lower frequency (≤ 3%). Of these, the most common TEAEs were abdominal distension, abdominal pain, vessel puncture site pain, and nausea.

The TEAEs experienced during the study were deemed mild (58 TEAEs, 85%) and moderate (10 TEAEs, 15%) in intensity. None of the subjects experienced a severe TEAE during the study.

No serious adverse events (SAE) and no deaths were reported for any of the subjects enrolled in this study. No subject was withdrawn by the investigator for safety reasons.

Clinical laboratory evaluation:

The main abnormal on-study laboratory values were minimal deviations of haematology values like Hkt, Hb, Neutrophils and platelets, as well as traces of blood and leukocytes in the urine. The judgements of “not clinically significant” are understandable from a clinician’s point of view (females being included).

One subject had positive serum beta HCG qualitative tests prior to dosing of period 2 and post study visits that were considered not clinically significant in the light of the quantitative beta HCG results (6.2 IU/L and 6.3 IU/L, respectively) and the subject being in menopausal state (8 years without menses according to the CRF). Menopausal beta HCG values are normally slightly higher (<7 IU/L) than pre menopause.

All other female subjects had negative pregnancy tests during the study.

All serology results were negative, all urine/breath drug screen results were negative and all tuberculin test results at screening were negative.

Vital signs, ECGs, physical findings

Generally, the subjects showed vital signs within normal range in both treatment groups. Slight tachycardia, and slightly elevated blood pressure values were presented and regarded as NCS what can be accepted from a clinician’s point of view. Results from the screening ECG assessments were considered normal or were judged normal variant – not clinically significant for subjects enrolled in this study. Physical examination findings were generally judged to be normal or without any changes, only in one subject, there was a clinically significant finding at the post study physical examination (i.e., gingival bleeding), that was resolving at the end of the study. Regarding the presented values, the judgements are understandable from a clinician’s point of view.

Concomitant Medications

Four subjects (4%) received concomitant medication during this study. Subject 033 applied 2 eye drops of Polysporin (polymyxin B [sulfate] /gramicidin) 7 times off site and 1 eye drop 3 times for mild conjunctivitis of the left eye, experienced following the administration of the reference in period 2. Subject 039 received Gravol (dimenhydrinate) once on-site for mild nausea (intermittent) and moderate vomiting, experienced following the administration of the Reference in period 2. Subject 070 received Tylenol (acetaminophen) once on-site for a moderate headache, experienced following the administration of the Test in period 2. Subject 085 received acetaminophen once off-site for a mild headache, experienced following the administration of the Test in period 1.The impact of the use of these medications was assessed and they were considered to have no impact on the pharmacokinetic evaluations of this study.

Study 2016-4130: A Multiple-Dose, Comparative Bioavailability Study of Two Formulations of Tacrolimus 5 mg Prolonged Release Capsules under Fasting Conditions

Methods

Study design

The study was an open-label, multiple-dose, randomised, two-period, two-treatment, two-sequence, crossover comparative bioavailability study, comparing two formulations of tacrolimus 5 mg prolonged release capsules (Tacforius 5 mg prolonged-release capsule (test) and Advagraf 5 mg prolonged-release hard capsule (reference)) in healthy male subjects under fasting conditions at steady state. The clinical part of the study took place from 31st of August 2016- 10th of October 2016

As tacrolimus is a prolonged release formulation with a long reported elimination half-life, concentrations may accumulate following repeated drug administration. As such, this study sought to assess the comparative bioavailability between a test and reference product under multiple dose, steady state conditions.

Based on the half-life of tacrolimus, it was expected that steady state would be attained by day 8.

Samples for the estimation of PK parameters were collected on Day 10, for which a sampling schedule was designed to ensure that the AUC_{tau}, $C_{max,ss}$, and C_{trough} parameters were adequately assessed at steady state from collected whole blood.

By implementing a crossover design, the estimated PK parameters for tacrolimus were compared within the same subject.

Subjects enrolled in this study were dosed in 3 groups on the following dates:

- Group 1 (Subjects 01-30)
    - Period 1: August 31, 2016;
    - Period 2: September 19, 2016.
- Group 2 (Subjects 31-60)
    - Period 1: September 07, 2016;
    - Period 2: September 26, 2016.
- Group 3 (Subjects 61-80)

- Period 1: September 11, 2016;
- Period 2: September 30, 2016.

Subjects were confined in-house from at least 10 hours prior to drug administration on Day 1 until at least 24 hours post-dose on Day 10 in each period.

A single 5 mg dose (one capsule) of the assigned drug product was administered according to the randomization scheme with 8 oz (±0.2 oz) of room temperature potable water from the morning of day 1 until the morning of day 10 (10 administrations in each period).

Subjects fasted from at least 10 hours prior to each drug administration until at least 4 hours post-dose.

In each period, 26 samples were collected as follows:

• On Days 1, 8, and 9: prior to dosing (0-hour);

• On Day 10: prior to dosing (0-hour) and at 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, and 24 hours post-dose.

The pre-dose sample on Day 1 was collected within 60 minutes of dosing. Pre-dose samples on Days 8, 9, and 10 were collected within 5 minutes of drug administration.

The chosen time points are regarded as adequate, since with an average Tmax (in fasting state) around 2 hours, this time was well covered, the 3 necessary time points for steady state were given and the 24 hour period on day 10 was in line with the recommended once daily administration (in the morning).

In line with the product specific EMA guideline for tacrolimus (EMA/CHMP/159744/2016), the analysed compound was tacrolimus (parent) and the analysed matrix was whole blood.

The washout period between drug administrations for each subject was 10 days between the last drug administration on Day 10 of Period 1 and the first drug administration on Day 1 of Period 2. The half-life of tacrolimus is long and variable. In healthy subjects, the mean half-life in whole blood, according to the originator's SmPC, is approximately 43 hours. Referring to the modified release guideline (EMA/CPMP/EWP/280/96 Corr1), even a possible direct switch from test to reference product and if steady state build up period is long enough, the 10 days of washout are acceptable.

This was an open-label study, but the samples that were shipped to the analytical laboratory did not contain treatment information on the sample label. Since blinding of the subjects or the clinical staff is not regarded necessary in a BE-study comparing PK parameters, the open-label conduct is acceptable.

Test and reference products

Product Characteristics	Test Product	Preference Product
Name	Tacrolimus 5 mg Prolonged-Release Capsules	Advagraf 5 mg Prolonged-Release Hard Capsules
Strength	5 mg	5 mg
Dosage form	Capsules	Capsules

Tacrolimus 5 mg manufactured at the proposed commercial manufacturing site has been compared to Advagraf (Tacrolimus) 5 mg manufactured by Astellas Ireland Co. The applicant also confirmed that the unit formula of the 5 mg biobatch is identical to the proposed commercial formulation.

Population studied

Study population consisted of 80 healthy, non-smoking, male volunteers, from 19 to 45 years of age, with a body mass index (BMI) between 18.9 and 29.9 kg/m2. Among the patients, 60 were Black, 18 White and 2 other. In principle, females using appropriate contraceptive methods could also have been included in this multiple dose study. But since the inclusion of both sexes is no defined prerequisite for BE-studies, it is deemed acceptable, that only males were included in this study.

A total of 80 subjects were included in this study and, after randomisation, 78 subjects received the test product and 71 subjects received the reference product. Five subjects were dismissed due to adverse events, four for non-compliance, three had out of range laboratory results at period 2 check-in and two withdrew for personal reasons. Hence, 66 subjects (24 in Group 1, 25 in Group 2, and 17 in Group 3) completed the study.

One subject completed both periods of the study; however, the subject's values were excluded from the PK analysis due to an AE (diarrhoea within 24 hours of Day 10 drug administration, as per protocol-specified criteria for removal) which was reported during post-clinical procedures.

PK population

Hence, 65 subjects were included in the PK and statistical data analyses.

Safety Population

The safety population included all of the subjects (80) who entered in the study.

Analytical methods

The analytical part of the study lasted from 06.10.2016 till 24.10.2016. The study samples were obtained stored at a nominal temperature of -25ºC. A total of 7416 samples from 80 subjects (26 time-points per subject, 2 periods, 2 treatments) were analysed, the theoretical amount of samples was 8320.

As regards Tacrolimus (analyte), internal standard was Tacrolimus 13CD3; samples were extracted from a 0.10 mL aliquot of K2EDTA human whole blood by liquid-liquid extraction. The extracted samples were injected into a liquid chromatograph. The detection method used was tandem mass spectrometry detector.

Quantitation is determined by peak area ratio method. A weighted (1/c2) linear regression is performed to determine the concentration of the analyte. The validated calibration range for the assay of Tacrolimus is from 0.2 ng/mL to 50.00 ng/mL.

The analytical method for the determination of Tacrolimus in human whole blood as well as respective validations were described adequately; the validations were performed according to the requirements of the EMA "Guideline on bioanalytical method validation" (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr 2*). Acceptance criteria are in a plausible range and were fulfilled.

The bioanalytical method demonstrated acceptable performance and was suitable for the determination of Tacrolimus in K_2EDTA human whole blood over the calibration range.

There were some concerns that the applicant clarified during the evaluation period. First one regarding the amount of the analysed samples and the second one due to a shoulder developed in some chromatograms for the sample and the ISTD.

Pharmacokinetic variables

The following pharmacokinetic parameters were estimated for whole blood tacrolimus using a non-compartmental approach in SAS® (version 9.3):

AUC_{tau}: The area under the analyte concentration versus time curve over one dosing interval (tau = 24 hours) as calculated by the linear trapezoidal method.

$C_{max,ss}$: Maximum measured analyte concentration over one dosing interval at steady state.

C_{trough} Measured concentration at the end of the dosing interval at steady state.

C_{pd}: Pre-dose (morning) measured analyte concentrations on Days 8, 9, and 10.

Fluctuation: Degree of fluctuation of the analyte concentration levels over one dosing interval: 100*(Cmax,ss – Ctrough)/(AUCtau/tau).

Swing: Degree of change of the analyte concentration levels over one dosing interval: 100*(Cmax,ss – Ctrough)/Ctrough.

C_{avg}: The average concentration: AUCtau/tau.

$T_{max,ss}$: Time of the maximum measured analyte concentration over one dosing interval.

Whole blood samples were assayed for tacrolimus. Based on these concentration levels, the PK parameters AUCtau, Cmax,ss, Ctrough, Cavg, Cpd, and Tmax,ss were estimated in order to characterize the extent and rate of absorption of the study drugs at steady state.

According to the modified release guideline (EMA/CPMP/EWP/280/96 Corr1), AUC(0-τau)ss, Cmax,ss, Cτau,ss are the parameters to be evaluated referring to bioequivalence of prolonged release products with accumulation for multiple dose studies.

Statistical methods

Descriptive statistics for the PK parameters of tacrolimus were calculated. Descriptive statistics include number of observations, arithmetic mean, standard deviation, geometric mean (where applicable), coefficient of variation (CV), median, minimum, and maximum.

Statistical analysis was performed on quality assured data from subjects in the statistical dataset. The PROC GLM procedure from SAS® (version 9.3) was used.

Three consecutive pre-dose concentrations (Cpd) on Days 8, 9 and 10, were analysed to assess the achievement of steady state. Statistical analysis revealed that both the day (p=0.835) and day-by-treatment (p=0.886) effects were not statistically significant, indicating that steady state levels were reached.

Analysis of Variance was performed on log-transformed AUCtau, Cmax,ss, and Ctrough. The significance of the sequence, period, treatment, and subject (sequence) effects was tested. Because this study was conducted in groups, the group factor was also considered in the statistical model.

Using the same statistical model, the least-squares-means, the differences between the treatments least-squares-means, and the corresponding standard errors of these differences were estimated for log-transformed AUCtau, Cmax,ss, and Ctrough parameters.

Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% CIs were calculated.

The 90% CIs of the relative mean whole blood tacrolimus AUCtau of the test to reference products should be between 90.00 and 111.11%.

According to the Applicant, the 90% CIs of the relative mean whole blood tacrolimus Cmax,ss and Ctrough of the test to reference products should be between 80.00 and 125.00%.

The criteria for evaluation proposed by the applicant are not fully in line with the respective EMA guidance, since the exemption for the 90%CI of Cmax in the normal BE range of 80.00-125.00% is only meant for single dose studies with tacrolimus.

Although peak whole blood levels do not seem to be critical for either safety or efficacy, narrowing of Cmax (and Ctrough) results (respective 90% CIs should lie between 90.00 and 111.11%) would be expected from a clinical point of view for the multiple dose study, since tacrolimus is a narrow therapeutic index drug and concentration differences at steady state are not as high as after a single dose.

But since the respective PK results were within the narrow acceptance range (Cmax [93.81-102.06], Ctrough (=Ctau,ss) [95.89-103.57]) this was acceptable.

Results

Table 8. Pharmacokinetic parameters for tacrolimus (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic <geometric> mean	**SD CV%**	**arithmetic <geometric> mean**	**SD CV%**
$AUC_{0\text{-}tau,ss}$	188.92 ng*h/mL <177.24 ng*h/mL>	70.52 37.33%	191.66 ng*h/mL <178.96 ng*h/mL>	75.75 39.53%
$C_{max,ss}$	14.14 ng/mL <13.14 ng/mL>	5.67 40.08%	14.30 ng/mL <13.40 ng/mL>	5.49 38.41%
$C_{tau,ss}$	5.70 ng/mL <5.28 ng/mL>	2.32 40.75%	5.70 ng/mL <5.25 ng/mL>	2.39 41.87%
$AUC_{0\text{-}tau,ss}$	area under the analyte concentration versus time curve over one dosing interval (tau = 24 hours)			
$C_{max,ss}$	maximum measured analyte concentration over one dosing interval. (at steady state)			
$C_{tau,ss}$	measured concentration at the end of the dosing interval			

Table 9. Statistical analysis for tacrolimus (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%*
$AUC_{(0\text{-}tau)}$	98.56	95.86-101.33%	9%
$C_{max,ss}$	97.85	93.81-102.06	14%
$C_{tau,ss}$	99.65	95.89-103.57	13%
* estimated from the Residual Mean Squares			

Bioequivalence could been shown between the 5 mg Test formulation and the 5 mg Reference product when administered as multiple dose under fasting conditions.

Protocol deviations

Slight deviations of blood sampling time points were not referred to as deviations in this study.

There were 4 protocol deviations in this study, which are depicted in the following table:

Table 10. Protocol deviations

Protocol Deviation Number	Protocol Section	Summary	Subjects Affected	Classification
2016-4130 P01	10.1 Restrictions	Subject 019 was found to have chewing gum in his mouth during the mouth check-in Period 1, Day 10 dosing. The subject was dismissed from the study.	019	Minor
2016-4130 P02	11.0 Criteria for Removal from the Study	This deviation was generated to address the contradicting statements in the protocol in order to clarify that additional subject may be enrolled, if required, to maintain statistical power required to demonstrate bioequivalence criteria as per Section 8.6 of the protocol.	N/A	Minor
2016-4130 P03	10.3 Tests/Procedures at Check-in	Carbon dioxide levels were obtained unnecessarily for subjects in Group 1 at Period 2 check-in.	001-030	Minor
2016-4130 P04	10.9 Vital Signs Measurements	Vital signs measurements on Day 10, time point 2 hours, were taken 2 minutes and 4 minutes early for Subjects 020 and 024, respectively.	020, 024	Minor

N/A, not applicable.

Since subject 019 subject did not act as agreed upon in the restriction information provided to and signed by the subjects included, dismissal is regarded as justified. Additional subjects were not enrolled; hence the second issue can be ignored. Additional measurement of CO2 levels does not cause any harm to neither the subjects nor the study, and is thus regarded as unproblematic. Vital signs measured 2 and 4 minutes too early are not at all regarded to affect the study outcome or to pose risks to the included subjects, and are thus regarded as unproblematic.

Safety data

A total of 80 subjects were included in the study. After randomization, 78 subjects received the Test (Tacforius) and 71 subjects received the Reference (Advagraf). All subjects who received at least one of the investigational products (n= 80) were included in the safety population.

An assessment of safety was based primarily on the frequency and severity of AEs, but also standard laboratory evaluations, vital signs, ECG findings, physical examination findings, and concomitant medication usage were evaluated.

Adverse events

Overall, there were 97 AEs involving 44 subjects (55.0% of subjects dosed), with thirty-one (31) subjects (39.7%) reporting a total of 60 AEs after administration of Treatment A and 23 subjects (32.4%) reporting a total of 37 AEs after administration of Treatment B. Of the 97 reported AEs, 75 AEs affecting 40 subjects were seen as reasonably related to the study drugs by the relevant investigators. Diarrhoea was the most prevalent AE in this study, with 23 occurrences affecting 16 subjects (20.0%). All reported diarrhoea events were mild in severity and deemed reasonably related to the study drugs. Six subjects experienced AEs which led to their discontinuation from the study, two of which were diarrhoeal events that occurred within the protocol-specified time interval for dismissal. The AEs resolved, were mild in severity, and were judged not to have impacted the subjects' safety. No deaths, SAEs, or other significant AEs occurred during the study.

Clinical laboratory evaluation:

Screening

Clinical laboratory tests for haematology, biochemistry, urinalysis, and serology were conducted at screening. All screening clinical laboratory tests results, including those of repeats, were either within normal range or not clinically significant (NCS) for all subjects prior to study entry. Screening tests for urine cotinine and urine drugs of abuse were conducted and all results were negative.

Check-In

Check-in tests for urine cotinine, breath alcohol, and urine drugs of abuse were conducted in each period. Two subjects (subjects 037 and 050) were dismissed from the study at Period 2 check-in due to having a positive test for urine cotinine. All other check-in tests for urine cotinine, breath alcohol, and urine drugs of abuse were negative.

In addition, clinical laboratory tests for CBC (complete blood count), liver function, metabolic panel (including renal function, calcium, magnesium, and potassium) were conducted for safety at Period 2 check-in. Three subjects (subjects 018, 022, and 030) were dismissed from the study due to health concerns as their check-in laboratory results (increase in creatinine, WBC, absolute neutrophil count and AST according to the CRFs) were out of range.

End of Study

Clinical laboratory tests for haematology, biochemistry, and urinalysis were conducted at the end of the study or after termination of a subject from the study. Six (6) clinically significant laboratory measurements were recorded as drug-related AEs, 5 of which resolved upon repeated measurement. One AE (blood bilirubin increased, Subject 024) remained unresolved as the subject failed to complete post-clinical laboratory repeat tests. All other post-study clinical laboratory tests results, including those of repeats, were either within normal range or not clinically significant (NCS).

Vital Signs, Physical Findings and Other Observations Related to Safety

Of the 97 reported AEs, 11 were related to vital signs.

Additionally, one subject reported dizziness approximately 1 hour after Day 6 dosing in Period 1 (Treatment B).

Vital signs were re-measured and results were within normal range.

There were 4 physical findings in this study: an arthropod bite, a vessel puncture site and rash, the latter reported for two subjects. All physical findings were unrelated to the administration of the study drugs.

There were no other significant findings related to vital signs, ECGs or physical examinations in this study.

Concomitant drug Therapy

There were no concomitant medications used during this study.

Conclusions

Based on the presented data obtained from the bioequivalence studies conducted by the applicant in support of this marketing authorisation application, Tacforius is considered bioequivalent with Advagraf.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available for Tacforius. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

To support this generic marketing authorisation application for Tacforius, three BE-studies have been conducted (single dose fed, single dose fasting and multiple dose fasting). The bioequivalence between the Tacforius 5 mg prolonged-release capsules and the reference product, Advagraf 5 mg prolonged-release capsules was demonstrated.

These 3 studies fulfilled the requests of the relevant EMA guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 ^{Corr1}) for prolonged release products with accumulation.

While applicable EMA guidance justifies the normal 80.00-125.00% acceptance range for the 90% CIs of Cmax for the single dose studies, this acceptance range for the 90% CIs of Cmax,ss and Ctau,ss is regarded as too wide for the multiple dose study. But since the GMRs of Cmax and Ctau,ss were clearly within the 90.00-111.11% acceptance interval, this was not an issue and bioequivalence was concluded for all 3 studies.

In vitro dissolution tests complementary to the BE studies were provided. The results do not perfectly fulfil the expectations of the BE-GL, since without high doses of surfactant, sink conditions were not reached with these prolonged-release capsules, making this method not very representative for in-vivo conditions. Nevertheless and according to the guideline the in vivo studies prevail in order to demonstrate BE. Therefore, BE was clearly demonstrated, hence, finally no great emphasis was put on these dissolution results from a clinical point of view.

To accept the BE studies done with the highest strength only, pharmacokinetic linearity over the whole dose range of Tacforius prolonged release capsule strengths should be shown and the CHMP requested further information in support of this assumed linearity. This was resolved accordingly with published literature and in-house data discussing in sufficient detail the extrapolation of the available pharmacokinetic data of various doses of Astagraf XL/Advagraf and showing the linkage between Prograf and Advagraf formulations. Therefore the biowaiver for the 3 lower strengths (0.5 mg, 1 mg and 3 mg) was accepted by the CHMP.

The safety profile of Tacforius is similar with that of the Reference medicinal product and hence, there is no need for additional risk minimisation measures. Tacforius is subject to restricted medicinal prescription, in the same way as the reference medicinal product.

2.4.6. Conclusions on clinical aspects

The CHMP considered that there were no objections for the approval of Tacforius 0.5 mg, 1 mg, 3 mg, 5 mg prolonged-release hard capsules from a clinical point of view.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Medication errors • Hypertension • Torsade de Pointes • Cardiac arrhythmias • Prolonged QT interval • Ventricular hypertrophy • Cardiomyopathies • Neurological and visual disorders • Diabetogenicity • Electrolyte changes • Galactose intolerance • Hepatic dysfunction • Renal dysfunction • Blood cell count changes • Coagulopathies • Use during pregnancy and lactation • GI perforation • Diarrhoea • Neoplasms • Serious infections and reactivation of pre-existing infections • Pure red cell aplasia (PRCA)
Important potential risk	• Interaction with MMF
Missing information	• None

Pharmacovigilance plan

There are no studies in the Pharmacovigilance Plan.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
IMPORTANT IDENTIFIED RISKS		
Medication errors	Labelling: Indication of correct use in SmPC **section 4.1**. **Section 4.2** of the SmPC states that this medicinal product should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients. Warning in **section 4.4** of the SmPC: Medication errors, including 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. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist. Medication errors are described in **section 4.8** of the SmPC. Prescription only medicine. The terms 'prolonged-release' and 'once daily' are prominent on the proposed blister, aluminium wrap and outer carton.	None
Hypertension	Labelling: Risk has been highlighted in the SmPC in **sections 4.4** and **4.8**. Prescription only medicine.	None
Torsades de Pointes	Labelling: Risk has been highlighted in the SmPC in sections **4.4, 4.8, and 5.3**. Prescription only medicine.	None
Cardiac arrhythmias	Labelling: Risk has been highlighted in the SmPC in sections **4.4, 4.8, and 5.3**. Prescription only medicine.	None
Prolonged QT interval	Labelling: Risk has been highlighted in the SmPC in sections **4.4, 4.8, and 5.3**. Prescription only medicine.	None
Ventricular hypertrophy	Labelling: Risk has been highlighted in the SmPC in sections **4.4, 4.8, and 5.3**. Prescription only medicine.	None
Cardiomyopathies	Labelling: Risk has been highlighted in the SmPC in sections **4.4, 4.8, and 5.3**. Prescription only medicine.	None

Neurological and visual disorders	Labelling: Warning in **sections 4.4, 4.5, 4.7, and 5.3 of the SmPC**. Listed in **section 4.8** of the SmPC. Prescription only medicine.	None
Diabetogenicity	Labelling: Warning in **section 4.4** of the SmPC. Listed in **section 4.8** of the SmPC. Prescription only medicine.	None
Electrolyte changes	Labelling: Risk has been highlighted in the SmPC in sections **4.4, 4.5 and 4.8**. Prescription only medicine.	None
Galactose intolerance	Labelling: Risk has been highlighted in the SmPC in **section 4.4**. Prescription only medicine	None
Hepatic dysfunction	Labelling: Warning in **section 4.4** of the SmPC. Listed in **section 4.8** of the SmPC. Prescription only medicine.	None
Renal dysfunction	Labelling: Risk has been highlighted in the SmPC in sections **4.4, 4.8, and 5.3**. Prescription only medicine.	None
Blood cell count changes	Labelling: Warning in **section 4.4** of the SmPC. Listed in **section 4.8** of the SmPC. Prescription only medicine.	None
Coagulopathies	Labelling: Risk has been highlighted in the SmPC in sections **4.4 and 4.8**. Prescription only medicine.	None
Use during pregnancy and lactation	Labelling: Risk has been highlighted in the SmPC in sections **4.6 and 5.3**. Prescription only medicine.	None
GI perforation	Labelling: Risk has been highlighted in the SmPC in sections **4.4 and 4.8**. Prescription only medicine.	None
Diarrhoea	Labelling: Risk has been highlighted in the SmPC in sections **4.4 and 4.8**. Prescription only medicine.	None
Neoplasms	Labelling: Risk has been highlighted in the SmPC in sections **4.4 and 4.8**. Prescription only medicine.	None
Serious infections and reactivation of pre-existing infections	Labelling: Risk has been highlighted in the SmPC in sections **4.4 and 4.8**. Prescription only medicine.	None
Pure red cell aplasia (PRCA)	Labelling: Risk has been highlighted in the SmPC in sections **4.4 and 4.8**. Prescription only medicine.	None
IMPORTANT POTENTIAL RISK		
Interaction with	Labelling: Risk has been highlighted in the SmPC in	None

MMF	**section 5.1**. Prescription only medicine.	
MISSING INFORMATION		
None		

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of tacrolimus prolonged-release hard capsules. The reference product Advagraf is indicated for the following indications:

- 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.

No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient.

From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview

on these clinical aspects based on information from published literature was considered sufficient.

The three bioequivalence studies hereafter form the pivotal basis:

a) Study TVY-P8-763: Single Dose 2-Stage Futility Crossover Comparative BA Study of Tacrolimus 5 mg Prolonged-Release Capsules in Healthy Male and Female Volunteers / Fed State

b) Study TVY-P7-885: Study Title: Single Dose 2-Stage Futility Crossover Comparative BA Study of Tacrolimus 5 mg Prolonged-Release Capsules in Healthy Male and Female Volunteers / Fasting State

c) Study 2016-4130: Study Title: A Multiple-Dose, Comparative Bioavailability Study of Two Formulations of Tacrolimus 5 mg Prolonged Release Capsules under Fasting Conditions

The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the EU requirements. Choice of dose, sampling points, overall sampling times as well as wash-out period were adequate. The analytical method was sufficiently validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Tacforius prolonged-release hard capsule met the protocol-defined criteria for bioequivalence when compared with the Advagraf prolonged release capsule. While applicable EMA guidance justifies the normal 80.00-125.00% acceptance range for the 90% CIs of Cmax for the single dose studies, this acceptance range for the 90% CIs of Cmax,ss and Ctau,ss was regarded as too wide for the multiple dose study. However, since the GMRs of Cmax and Ctau,ss were clearly within the 90.00-111.11% acceptance interval, this was accepted and bioequivalence was demonstrated for all 3 studies.

In order to accept the biowaiver, PK dose-linearity should be shown in the whole dose range. Thus, the CHMP requested the applicant to provide additional information supporting the dose linearity for the lowest strength. This issue was resolved satisfactorily with published literature and in-house data, providing enough information to expect linear pharmacokinetics over the whole dose range (0.5 mg – 10 mg) of tacrolimus. Therefore, the biowaiver for the 3 lower strengths (0.5 mg, 1 mg and 3 mg) was accepted by the CHMP.

A benefit-risk balance comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tacforius is favourable in the following indication:

- 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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