14 November 2024
EMA/554250/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

CellCept

International non-proprietary name: Mycophenolate mofetil

Procedure No. EMEA/H/C/000082/II/0170/G

Note

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

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List of abbreviations

ABOi	blood group incompatible
AcMPAG	acylglucuronide of MPA
ADR	adverse drug reaction
AE	adverse event
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}12h}$	area under the plasma concentration-time curve from time 0 h to time 12 h
AZA	Azathioprine
BCRP	Breast cancer resistance protein
b.i.d.	twice a day (bis in die)
BSA	body surface area
CAV	cardiac allograft vasculopathy
CHD	congenital heart disease
C_{max}	maximal plasma concentration
C_{trough}	concentration at the end of a dosing interval, prior to a next dose
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CsA	ciclosporin A
CSR	Clinical Study Report
EBV	Epstein-Barr virus
EC_{50}	half maximal effective concentration
ELTR	European Liver Transplant Registry
EHC	enterohepatic recirculation
EMA	European Medicines Agency
EMB	endomyocardial biopsy
EMIT	enzyme multiplied immunoassay technique
ERA	Environmental risk assessment
EU	European Union
Eve	everolimus
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HLA	human leukocyte antigen
HSCT	haematopoietic stem cell transplantation
HTx	heart transplant(ation)
IBD	International Birth Date
ICSR	Individual Case Safety Report
IH	isohemaglutin

IMPDH	inosine monophosphate dehydrogenase
ILTS	International Liver Transplantation Society
ISHLT	International Society for Heart and Lung Transplantation
IV	intravenous
LTx	liver transplant(ation)
MAH	Marketing Authorisation Holder
MDR1	multidrug resistance protein 1
MMF	mycophenolate mofetil
MPA	mycophenolic acid
MPAG	phenolic 7-O-glucuronide of MPA
MRP2	multidrug resistance-associated protein 2
OATP	organic anion transporting polypeptide
OPTN	Organ Procurement and Transplantation Network
PD	pharmacodynamic(s)
PBMC	peripheral blood mononuclear cell
PELD	paediatric end-stage liver disease
PK	pharmacokinetic(s)
PTLD	post-transplant lymphoproliferative disorder
popPK	population pharmacokinetics
RTx	renal transplant(ation)
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPLIT	Society of Pediatric Liver Transplantation
SRTR	Scientific Registry of Transplant Recipients
TAC	tacrolimus
T_{max}	time to maximum concentration
UGT	uridine diphosphate glucuronosyltransferase
UK	United Kingdom
US	United States

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 31 May 2023 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	Type IB	I, II and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

C.I.6.a: Extension of indication to include paediatric patients (3 months to 18 years of age) for hepatic and cardiac transplants and to extend the indication for renal transplants for paediatric patients starting from 3 months, based on pharmacokinetic data, published literature and the Roche Global Safety Database. As a consequence, sections 4.1, 4.2, 4.8 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly.
Type IB (C.I.z): Update of the precautions to be taken before handling or administering the medicinal product in section 4.2 of the SmPC for the CellCept 500 mg tablets formulation in order to be in line with the other CellCept formulations. The Package Leaflet is updated to cross reference section 2 in section 6 for sodium content, in line with the QRD guidance.
In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and bring the PI in line with the latest QRD template version 10.3.

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

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Thalia Marie Estrup Blicher Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	31 May 2023
Start of procedure:	17 June 2023
CHMP Rapporteur Assessment Report	18 August 2023
CHMP members comments	n/a
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 September 2023
Request for supplementary information (RSI)	14 September 2023
CHMP Rapporteur Assessment Report	21 February 2024
PRAC Rapporteur Assessment Report	21 February 2024
PRAC Outcome	7 March 2024
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	15 March 2024
2nd Request for supplementary information (RSI)	21 March 2024
CHMP Rapporteur Assessment Report	22 June 2024
PRAC Rapporteur Assessment Report	22 June 2024
PRAC members comments	04 July 2024
Updated PRAC Rapporteur Assessment Report	08 July 2024
PRAC Outcome	11 July 2024
CHMP members comments	11 July 2024
Updated CHMP Rapporteur Assessment Report	19 July 2024
3rd Request for supplementary information (RSI)	25 July 2024
CHMP Rapporteur Assessment Report	17 September 2024
PRAC Rapporteur Assessment Report	17 September 2024
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	27 September 2024
PRAC Outcome	03 October 2024
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	n/a
4th Request for supplementary information (RSI)	17 October 2024
CHMP Rapporteur Assessment Report	30 October 2024
PRAC Rapporteur Assessment Report	30 October 2024
PRAC members comments	n/a

Timetable	Actual dates
CHMP members comments	n/a
Updated PRAC Rapporteur Assessment Report	07 November 2024
Updated CHMP Rapporteur Assessment Report	07 November 2024
CHMP Opinion	14 November 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Heart transplantation (HTx)

Congenital heart disease (CHD, also referred to as congenital cardiomyopathy) is the most common underlying diagnosis in infants younger than 1 year of age, representing a diverse group of diseases that can lead to transplantation. Among older patients, cardiomyopathy remains the predominant cause for HTx. Paediatric HTx accounts for approximately 14% of the total HTx worldwide (Dipchand et al. 2013) The number of paediatric HTx reported to the International Society for Heart and Lung Transplantation (ISHLT) registry has increased over time to 442 in 2004, 586 in 2014, and 684 in 2015 (Rossano et al. 2016). In 2019, there were 507 paediatric HTx performed in the US (14%), in patients up to 17 years of age (OPTN 2020).

Liver transplantation (LTx)

The number of LTx in Europe recorded in the European Liver Transplant Registry in 2019 was 4,719 and paediatric LTx (less than 18 years) in Europe account for approximately 10% of the LTx annually (around 500 paediatric LTx in 2019). Over the past decade, recipient age, sex, and racial distributions have changed little. As in previous years, cholestatic biliary atresia remained the leading cause of liver failure. Children are typically undergoing transplant at higher acuity than in the past and this is likely due to the lack of suitable donor organs. Blood group incompatible (ABOi) LTx occurred in 5.4% of recipients in 2017-2019, an increase from 3.5% in the previous era (Kwong et al. 2021).

State the claimed therapeutic indication

New text (in bold and underlined):

*CellCept is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in **adult and paediatric (3 months to 18 years of age)** patients receiving allogeneic renal, cardiac, or hepatic transplants.*

Management

Immunosuppression therapy is used to prevent rejection of the donor organ thereby enabling organ and patient survival. It is commonly separated into induction therapy (given at time of transplant), maintenance therapy (chronic medications), and acute rejection therapy (for the treatment of acute complications).

The model of alloimmune response, involving both naïve and memory lymphocytes, in the rejection of transplanted organs has been described in detail in the literature (Halloran et al. 2004). Rejection episodes are not an organ-specific complication and can occur for any transplanted organ. Additionally, there is little evidence to suggest that the mechanism of rejection is different in adults compared with children.

CellCept, in combination with ciclosporin and corticosteroids, is currently indicated in the EU for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac, or hepatic transplants, including children from 2 years of age with renal transplants. No dosing recommendation is available in paediatric population for use in cardiac or hepatic transplant. However, CellCept is used off-label in the paediatric population with liver and heart transplants and in renal transplant patients below 2 years of age and most maintenance immunosuppressive protocols in children are similar to the protocols used in adults and employ a three-drug regimen consisting of a calcineurin inhibitor (CNI) (such as Cyclosporin A (CsA) or tacrolimus (TAC)), an antimetabolite agent (mycophenolate mofetil (MMF) or less commonly azathioprine (AZA)), and tapering doses of glucocorticoids over the first year post transplantation (Kobashigawa et al. 2006; Costanzo et al. 2010). Hence, there is an unmet need for approved medicinal product for prophylaxis of transplant rejection in paediatric patients.

2.1.2. About the product

Mycophenolate mofetil is the 2-morpholinoethyl ester of mycophenolic acid (MPA). MPA is a selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines whereas other cell types can utilise salvage pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells.

In addition to its inhibition of IMPDH and the resulting deprivation of lymphocytes, MPA also influences cellular checkpoints responsible for metabolic programming of lymphocytes. It has been shown, using human CD4+ T-cells, that MPA shifts transcriptional activities in lymphocytes from a proliferative state to catabolic processes relevant to metabolism and survival leading to an anergic state of T-cells, whereby the cells become unresponsive to their specific antigen.

Mycophenolate mofetil (MMF, CellCept) has been available to prescribers in the EU for more than 20 years and has remained an established component of immunosuppression protocols over this time.

CellCept was first granted marketing approval in the United States (US) on 3 May 1995 for the prophylaxis of RTx rejection in adults receiving allogeneic RTx. On 14 February 1996, the initial Marketing Authorisation in the EU was granted for the prophylaxis of RTx rejection in adults. On 17 August 1998, Cellcept was approved for cardiac transplant (EMEA/H/C/00082/II/0010), and on 09 November 2000 for liver transplant (EMEA/H/C/00082/II/0024) in the EU. The product was subsequently approved in 119 countries worldwide. On 16 July 2001, the European Medicines Agency (EMA) approved the prevention of acute rejection for the paediatric RTx population aged 2 to 18 years (procedure EMEA/H/C/00082/II/0027).

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

No scientific advice was given.

2.2. Non-clinical aspects

2.2.1. Introduction

Mycophenolate mofetil (MMF) is a prodrug, that hydrolysed to 2-morpholinoethyl ester of Mycophenolic acid (MPA) is an immunosuppressive agent. MMF has 1.3 to 2.36 times higher oral bioavailability than

MPA and is rapidly and fully hydrolysed to MPA in the liver and intestine. Thus, pharmacologically active MPA levels are reached subsequent to MMF dosage of three-quarters to less than one-half of the corresponding amount of MPA.

At the time of MA approval, no Environmental Risk Assessment (ERA) was required. Moreover, CellCept has not been re-registered in Europe since such requirements came into force (2006). In order to fulfil the requirements of an extension to a paediatric indication a full ERA with the existing data, partially assessed in compliance with GLP, was submitted. Since MMF is rapidly and fully hydrolysed to MPA in the liver and intestine, the ERA has been performed for the pharmacologically active substance mycophenolic acid (MPA). Further to the CHMP request, the ERA has been performed according to the revised EMA Guideline on ERA for Human Non-GMO Medicines (EMEA/CHMP/SWP/4447/00 Rev.1) of 15 February 2024.

No new data was provided on the pharmacology, pharmacokinetics or toxicology of MMF.

2.2.2. Ecotoxicity/environmental risk assessment

Phase I: Initial screening and exposure estimation

A PBT screening was carried out. The method used to determine the $logD_{ow}$ values was non-GLP, non-OECD. However, the method followed the principles of the shake-flask method according to OECD 107. The $logD_{ow}$ values are below the Phase I trigger value of 4.5 according to the EMA guideline and no further PBT assessment is thus warranted.

In a risk assessment of surface water, the potential environmental risks of MPA were evaluated using the default factors as stated in EMA guidance on ERA. The predicted environmental concentration for the surface water PEC_{SW} while using the default FPEN of 0.01 was calculated as 11 µg/L, which exceeds the phase I trigger value of 0.01 µg/L.

Trigger values for soil

For triggering a risk assessment for the soil compartment the PEC_{SW} was used in combination with the organic carbon normalised adsorption partition coefficient (K_{OC}). Because the highest $K_{OC,SLUDGE}$ for MPA is 37 L/kg (i.e. <1,000 L/kg), no soil risk assessment is required.

Trigger values for groundwater

A risk assessment for groundwater via bank filtration was triggered for MPA since the $K_{OC,SLUDGE}$ is 37 L/kg (i.e. ≤10,000 L/kg), and MPA is not readily biodegradable. Because a soil assessment is not triggered, no risk assessment for groundwater via pore water is required.

Trigger values for secondary poisoning

With measured n-octanol/water distribution coefficient ($logD_{OW}$) values of 2.28 at pH 5, 0.48 at pH 7 and -1.69 at pH 9 (i.e. <3) a risk assessment for secondary poisoning is not required.

Phase II: Environmental fate and effects analysis

Tier A: Initial environmental fate and effects analysis

In order to evaluate the potential risks to the environment from the use of the MPA, phase II Tier A ERA studies reported in **Table 1** have been conducted with MPA. PNEC values were derived accordingly based on the identified NOEC/EC10 values.

Table 1: List of OECD/ISO studies with MPA.

Study	Protocol
Algae and Cyanobacteria growth inhibition study	OECD 201
Daphnid sp. Reproduction study	OECD 211
Shortened life-cycle study with zebrafish	OECD 229/210
Adsorption-Desorption test using batch equilibrium method	OECD 106
Biodegradation in activated sludge	OECD 314B
Inbibition of nitrification of activated sludge micro-organisms	ISO 9509 (1989)
Respiration inhibition study with activated sludge	OECD 209
Biodegradation study	OECD 301 F

The MAH submitted a non-GLP study conducted according to ISO 9509 (1989) to investigate the inbibition of nitrification of activated sludge micro-organisms by chemicals and waste waters, used to derive the PNEC for micro-organisms in STP. The NOEC for inhibition of nitrification was determined to be 27.8 mg/L.

In addition, in a GLP study according to OECD 209 conducted in 1999, the 3h effect values EC10 = 69 mg/L, EC20 = 164 mg/L and EC50 = 2213 mg/L were derived.

Two water/sediment fate studies according to FDA 3.11 from 1994 and 1995 were provided. These studies were performed at very high dosages, 1 and 5 mg MMF/L, respectively. These dosages are about a factor 2,200 (for 1 mg/L dosage) and a factor 11,000 (for 5 mg/L dosage) higher than the calculated PEC_{SW}. At the lower dose of 1 mg/L only 5.5% of the applied radioactivity was bound to sediment, whereas the values was slightly above 10% (11.2%) at the high dosage of 5 mg/L. Especially in the study with the carboxyl-14C labelled MMF a high mineralisation of about 60% was observed. It was assumed that the metabolite (presumably 14C-MPA) was easily biodegradable. This is in conformance with the high mineralisation observed with carboxyl-^{14}C labelled MPA in the biodegradation in activated sludge study. In view of the high mineralisation rate in sediment/water studies and the low DT_{50} values in the activated sludge study (1.7 days for primary and 2.9 d for ultimate degradation) a sediment toxicity test was considered not be required.

Biodegradability. A non-GLP study on ready biodegradability was performed on Mycophenolate mofetil (MMF, prodrug) according to OECD 301 F (BMG study no. 337/a-05), demonstrating that the substance is not readily biodegradable (4.3% biodegradation after 28 days).

K_{OC} – soil fate and effects assessment. Adsorption constants to the organic carbon fraction in three soils and two activated sewage sludges were determined following OECD guideline 106 using 14C-labelled MPA. The average K_{OC} (range in brackets) was 348 (168–557) L/kg in all three soils and 33.5 (30–37) L/kg in both sludges, respectively. The experimental data show that MPA will not adsorb to organic substrates. Based on the single and average adsorption constants for various soils and sewage sludges, MPA can be classified as low to medium mobile in soils and having a very high mobility in sewage sludges

according to the McCall classification scheme. Hence, no consideration of the soil compartment through landspreading of sewage sludge is necessary for MPA.

Algae growth inhibition study. An OECD 201 test (conducted in 1999) over 96 hours was performed in compliance with GLP with the green algae *Raphidocelis subcapitata*. The 96 h EC10 value was 12 µg/L GMC based on growth rate.

Cyanobacteria growth inhibition study. A cyanobacteria study according to OECD 201 and over 72 hours was performed with MPA in compliance with GLP with the cyanobacteria *Anabaena flos-aquae*. The 72 h EC10 value based on growth rate was 155 µg/L GMC.

Daphnid reprotoxicity study. An OECD 211 test in compliance with GLP was performed with MPA with *Daphnia magna* under semi-static media exchange conditions over 21 days. The lowest NOEC for *Daphnia magna* for reproduction/fecundity is 0.929 mg/L (i.e. 929 µg/L) MMC.

Fish, short-term reproduction assay. This GLP test was based on a detailed review paper of the OECD about fish life-cycle tests taking into account relevant aspects of the OECD guidelines 229 and 210. The aim of the study was to determine lethal and sub-lethal effects of MPA on the reproduction of mature *Danio rerio* (zebrafish) and on survival and growth of the early-life stages of this species. To achieve this, a series of concentrations of the test item in aqueous solution was prepared. The test organisms were exposed to these concentrations as well as to controls without the test item. During the test period the test solutions were renewed in a flow-through system. The NOEC was 10.9 µg/L based on mortality (post-hatch survival) and on numbers of healthy fish of the F1 generation while the EC10 was established at 5.8 µg/L.

Tier A Risk assessment

Surface water:

As the phase I surface water assessment was above the trigger value of 0.01 µg/L, the MAH calculated a refined PEC_{SW} using consumption data in a phase II A assessment. The MAH provided consumption data from France, Germany, Italy, Spain and UK from IQVIA in the years 2018-2022. Consumption was largest in the UK in 2021 (331.5 mg/inhabitant/year), and this value was used to refine the PEC_{SW}. Using the equation Specific consumption / (365 d x default wastewater per inhabitant x default dilution) a refined PEC_{SW} was determined as 0.454 µg/L.

$$\begin{aligned} PEC_{SW\text{-}REFINED} &= \text{Specific consumption} \div (365\ \text{d x default wastewater per inhabitant} \times \text{default dilution}) \\ &= 331{,}500\ \mu g/y \div (365 \times 200\ l/d \times 10) \\ &= 0.454\ \mu g/l \end{aligned}$$

For MPA a study for biodegradation in surface water according to OECD 314B was performed. Using the assessed $DegT_{50}$, primary value of 1.7 days, a biodegradation rate k of 0.017 h^{-1} was calculated. Using this value in SimpleTreat 4.0, this results in a removal rate of MPA in sewage treatment of 0.118 (i.e. 11.8%).

Applying the removal rate to the value of 0.454 µg/L resulted in a $PEC_{SW\text{-}REFINED}$ with removal in sewage treatment of 0.401 µg/L.

The surface water predicted no-effect concentration $PNEC_{SW}$ was calculated as the lowest of the chronic surface water ecotoxicity EC10/LC10 values of 5.8 µg/L for fish divided by an assessment factor of 10. This results in an $PNEC_{SW}$ of 0.58 µg/L.

$PNEC_{SW}$ = 5.8 µg/L ÷ 10 = 0.58 µg/L

The surface water PEC÷PNEC risk characterisation ratio (RCR_{SW}) using the PEC_{SW} based on consumption data and elimination in sewage treatment of 0.401 µg/L and the $PNEC_{SW}$ of 0.58 µg/L as derived above was:

RCR_{SW} = 0.401 µg/L ÷ 0.58 µg/L = 0.69

The resulting value of a RCR_{SW} of 0.69 did not exceed the trigger (i.e. <1) and therefore a risk caused by MPA to surface waters was not to be expected.

Risk assessment for sediment:

The PEC_{SED} was derived using Eq. 14–17 as well as default values of the revised EMA Guidance Document. The PEC_{SED} is based on adsorption to suspended solids. In view of many default values, the PECSED ultimately depends on the (K_{OC}) and on the surface water PEC (PEC_{SW}). The PEC_{SED} for the risk assessment is derived for the maximum K_{OC} in soil (i.e. 575 L/kg) as a worst case.

PEC_{SED}, dry weight = PEC_{SED}, wet × 4.6 = 0.005 mg/kg × 4.6 = 0.024 mg/kg dry weight

The sediment PNEC will be derived from a chronic sediment ecotoxicity test with larvae of the midge Chironomus riparius, following OECD guideline 218 and performed in compliance with GLP. A study according to OECD 218 with the sediment dweller Chironomus riparius will be performed as a post-marketing commitment.

Risk assessment for sewage treatment plant:

The sewage treatment PEC (PEC_{STP}) was approximated as the surface water PEC multiplied by 10 (the default surface water dilution factor used in the PEC_{SW} calculation):

PEC_{STP} = 0.401 µg/L × 10 = 4.01 µg/L = 0.00401 mg/L

The bacterial PNEC for sewage treatment ($PNEC_{STP}$) was calculated as the respiration inhibition EC10 of 69 mg/l divided by an assessment factor of 10:

$PNEC_{STP}$ = 69 mg/L ÷ 10 = 6.9 mg/L

Hence, the sewage treatment PEC÷PNEC risk characterisation ratio (RQ_{STP}) is calculated as:

RQ_{STP} = 0.00401 mg/L ÷ 6.9 mg/L = 0.0006

In conclusion the PEC÷PNEC risk characterisation ratio of 0.0006 does not indicate a risk caused by MPA to sewage treatment.

Risk assessment for groundwater (via bank filtration):

The groundwater PEC (PEC_{GW}) is approximated in a Tier A assessment as the PECSW divided by 4. The groundwater PNEC ($PNEC_{GW}$) was derived from the $PNEC_{SW}$ of 0.58 µg/L divided by an additional assessment factor of 10.

The groundwater PEC÷PNEC risk characterisation ratio (RCR_{GW}) was calculated as follows:

$RCR_{GW} = PEC_{GW} \div PNEC_{GW}$

$RCR_{GW} = (PEC_{SW} \div 4) \div (PNEC_{SW} \div 10)$

RCR_{GW} = (0.401 µg/L ÷ 4) ÷ (0.58 µg/L÷ 10) = 1.73

The MAH concluded that in view of an RCR_{GW} of 1.73 a potential risk caused by MPA to groundwater cannot be excluded. A Tier B assessment for the groundwater was triggered.

If the RQ_{GW} is ≥1, further evaluation is needed in Tier B. Because the PEC_{SW} was already refined, a further refinement of the PEC_{GW} was performed by a groundwater modelling for a realistic worst-case scenario according to SiMBaFi – a bank filtration simulation model.

The refined groundwater PEC÷PNEC risk characterisation ratio (RCRGW-REFINED) was calculated:

$RCR_{GW\text{-}REFINED} = PEC_{GW\text{-}REFINED} \div PNEC_{GW}$

$RCR_{GW} = PEC_{GW\text{-}REFINED} \div (PNEC_{SW} \div 10)$

$RCR_{GW} = 0.115\ \mu g/L \div (0.58\ \mu g/L \div 10) = 1.99$

As result for the Tier B groundwater risk assessment, a potential risk caused by MPA to groundwater cannot be excluded.

Summary of main study results

Substance (INN/Invented Name): Mycophenolic acid (MPA)			
CAS-number (if available): 24280-93-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log D_{ow}	Shake-flask method (non-GLP)	$logD_{ow}$ at pH 5 = 2.28 $logD_{ow}$ at pH 7 = 0.48 $logD_{ow}$ at pH 9 = -1.69 pKa1 = 4.58 (COOH) pKa2 = 8.04 (phenol)	Not PBT ($logD_{ow}$ < 4.5)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	logD_{ow}	$logD_{ow}$ at pH 5 = 2.28 $logD_{ow}$ at pH 7 = 0.48 $logD_{ow}$ at pH 9 = -1.69	Not Bio-accumulative (B) ($logD_{ow}$ < 3)
	BCF	Not determined	-
Persistence	OECD 301F	Not readily biodegradable	P
Toxicity	NOEC (fish) CMR substance (MPA)	0.00132 mg/L	T
PBT-statement :	The compound is not considered a PBT substance		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC_{SW}, default	11	µg/L	> 0.01 threshold
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	$K_{OC\ ads}$ for soil: 348 (168-557) L/kg $K_{OC\ ads}$ for sludge: 33.5 (30-37) L/kg	KOC < 10,000 L/kg
Ready Biodegradability Test	OECD 301 F	Not readily biodegradable	-
Aerobic and Anaerobic Transformation in Aquatic Sediment systems (MP-SW system)	OECD 308	Not performed	-
Phase IIa Effect studies			

Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/Green algae (*Raphidocelis subcapitata)*	OECD 201	ErC_{10} NOErC EyC_{10}	12.0 9.0 8	µg/L	(Growth Rate) (Biomass) *not acceptable*
Algae, Growth Inhibition Test/Blue-green algae (*Anabaena flos-aquae*)	OECD 201	EC_{10} NOEC	155 83.9	µg/L	Growth Rate
Daphnia sp. Reproduction Test	OECD 211	EC_{10} NOEC	929 630	µg/L	
Fish, short-term reproduction assay (extended)/ *Danio rerio* (zebrafish)	Extended OECD 229	NOEC EC_{10}	1.32 5.8	µg/L	Growth F1 Mortality F1
Activated Sludge, Respiration Inhibition	OECD 209	EC_{10}	69	mg/L	Total respiration
Sediment dwelling organisms	OECD 218	NOEC		mg/kg	Pending

2.2.3. Discussion on non-clinical aspects

Only data regarding the environmental risk assessment (ERA) have been submitted in this application, which was considered acceptable by the CHMP. Several GLP-compliant OECD as well as non-GLP, non-OECD studies were submitted to support the environmental risk assessment of MMF/MPA.

Some studies required according to the EMA guideline on ERA were not submitted and others were deemed not acceptable due to the design of the studies. An updated ERA should be provided taking the new studies into account. Also, the risk assessment for the aquatic compartment is not accepted as the most sensitive NOEC should be used, which results in a risk for this compartment. This should also be included in an updated ERA.

Hence, at the CHMP request, the MAH submitted an updated ERA in compliance with the guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 Rev. 1) published on 15 February 2024. In the study on biodegradation in water (#41485) more than 10% of applied radioactivity was bound to the sediment at test end. This sorption behaviour was confirmed in the study on biodegradation in activated sludge (OECD 314 B) where again more than 10% AR was bound to the sludge as NER on day 14. Hence, a study on toxicity to sediment swelling organisms (e.g. OECD 218) was deemed necessary. The MAH provided a letter of agreement to provide a study on toxicity to sediment dwelling organisms according to OECD 218 by Q1 2026, as requested, which is considered acceptable by the CHMP.

As result of the risk assessment, a potential risk caused by MPA to groundwater cannot be excluded. Therefore, precautionary and safety measures are included in sections 5.3 and 6.6 of the summary of product characteristics (SmPC).

The MAH calculated a refined PEC surface water value based on consumption data from 2018-2022 in the (EU) country with the highest consumption. The method is considered acceptable according to ECHA guidelines, and a refined PEC_{SW} was established at 0.454 µg/L. However, the risk assessment for the aquatic compartment should be updated and re-submitted using the most sensitive effect value NOEC = 1.32 µg/L. Using the most sensitive NOEC value from the extended OECD 229 study, a risk for the aquatic compartment is identified. The MAH acknowledges that there is also a risk to surface water for fish using the NOEC of 1.32 µg/L. The ERA report and SmPC will be amended by Q1 2026.

2.2.4. Conclusion on the non-clinical aspects

The updated data submitted in this application lead to a significant increase in environmental exposure further to the use of MMF/MPA.

- Considering the above data, MMF/MPA should be used according to the precautions stated in the SmPC in order to minimize any potential risks to the environment.

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

The MAH should provide a study on toxicity to sediment dwelling organisms according to OECD 218 by Q1 2026. In addition, the MAH should update and re-submit the risk assessment for the aquatic compartment using the most sensitive effect value by Q1 2026

2.3. Clinical aspects

2.3.1. Introduction

GCP

The MAH 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.

- Tabular overview of the MAH sponsored paediatric clinical pharmacology studies, paediatric clinical studies and retrospective studies reported in the scientific literature

Paediatric kidney transplantation:

Table 2 Comparative Data: Paediatric Kidney Transplantation (Roche Study reports)

Study / Reference*	Study Design	Formulation/ Dosing	Demographics (number of patients; gender; age; other details)	Key Findings
Study MYC2190 (Roche Study Report P-180191)	Non-randomised multi-centre, open-label dose-ranging PK, Safety and Tolerance study in prevention of rejection in paediatric renal allograft recipients (3 age groups, 3 dose groups per age group). Intended duration: 3 years; early termination. PK evaluated for each patient during the first year of the study.	IV: vials with 500 mg MMF equiv. [IV administration abandoned due to unavailability of formulation] Oral: capsules: 50 mg, 250 mg (for batch ID see Roche Report) MMF dose groups: 15, 23, 30 mg/kg b.i.d. CellCept	40 (27 males, 13 females) first or second renal allograft recipients enrolled into one of three defined age groups; Age: 3 mo -18 yrs; 8 patients <6 yrs, 15 patients 6-<12 yrs, 17 patients 12-18 yrs. Evaluable subjects for key PK data:	1. The dose predicted to provide a MPA AUC_{0-12h} closest to the target exposure of 27.2 h·µg/mL was 600 mg/m². 2. Doses calculated based on estimated BSA reduced the CV by about 10% - hence dosing based on BSA preferred over dosing based on body weight.

Age (yrs)	Dose (mg/kg)	n Day 14	n Day 21
<6	15	7	6
	23	1	1
	30	–	–
6-<12	15	4	5
	23	4	5
	30	4	5
12-18	15	7	7
	23	6/5	5
	30	3	3

Study / Reference*	Study Design	Formulation/ Dosing	Demographics (number of patients; gender; age; other details)	Key Findings
Study MYCS2675 (Roche Report P-180263)	Non-randomised multi-centre, open-label, single arm study of MMF oral suspension in paediatric recipients of renal allografts. Patients followed for 3 yrs post-Tx.	Patients received MMF oral suspension (for batch ID see Roche Report) 600 mg/m² b.i.d., up to 1 g b.i.d. After study Month 9 patients were allowed to switch to MMF 250 mg capsules formulation	100 first or second renal allograft recipients enrolled into one of three defined age groups: 33 patients aged 3 months to <6 yrs, 34 patients aged 6 to <12 yrs, and 33 patients aged 12–18 yrs. A total of 17, 17, and 21 patients from these respective age groups participated in the PK portion of the study.	1. Confirmation of paediatric dosing recommendation 2. No clinically significant differences in MPA and MPAG PK parameters among the three defined age groups. 3. A dosing regimen of MMF 600 mg/m² b.i.d. achieved the targeted early Tx (Day 7) MPA AUC_{0-12h} (27.2 h·mg/L). 4. A 1.9-fold higher mean dose-adjusted MPA AUC_{0-12h} observed in the later post-Tx period (Day 7 vs. Month 3 post-Tx for all patients).
Assessment of Relevance The extrapolation from adult heart and liver transplant patients to paediatric heart and liver transplant patients heavily relies on the comparison of adult and paediatric kidney transplant patients and the derived similarities between these populations in the pharmacokinetics and pharmacodynamics of MMF and its metabolites. The paediatric MAH-sponsored kidney transplantation program consisted of two paediatric studies, an initial dose-ranging pilot study (Study MYC2190) and a single pivotal study (Study MYCS2675), enrolling a total of 140 paediatric renal transplant patients (3 months and 18 years of age); all patients in these two studies received MMF. Study MYCS2675 provided the basis for the labelled dose recommendation of 600 mg/m² b.i.d. for the prophylaxis of rejection in paediatric renal allograft patients.				

AUC_{0-12h}=area under the concentration-time curve from time 0 h to 12 h; b.i.d.=twice a day; MMF=mycophenolate mofetil; MPA=mycophenolic acid; MPAG=mycophenolic acid phenolic glucuronide; PK=pharmacokinetic(s); Tx=transplant(ation); yrs=years.

Table 3 Comparative Data: Paediatric Kidney Transplantation (Literature References)

Key Evidence				
Literature Reference*	**Study Design**	**Formulation/ Dosing**	**Demographics (number of patients; gender; age; other details)**	**Key Findings**
Filler et al. 2000	AUC and trough level MPA measurements in three groups of paediatric renal Tx recipients: without CNI, with CsA, with TAC (all besides steroids) to elucidate the influence of the concomitant CNI on the PK of MMF.	Dose guided by target pre-dose trough concentration to be achieved (2-5 mg/L); resulting dose in group with no CNI (n=13): 866 ± 401 mg/m²/day; in group co-treated with TAC (n=14): 555 ± 289 mg/m²/day; in group with CsA (n=15): 1158 ± 301 mg/m²/day.	42 patients; mean ± SD age: at Tx 11.7±3.4 yrs, at investigation 14.4±4.0 yrs	1. Pharmacokinetics of MMF are influenced by type of concomitant immunosuppression. 2. The mean dose in order to achieve the same AUC of 60 h·mg/L without CNI co-treatment 500 mg/m² b.i.d.; with TAC co-treatment dose had to be significantly reduced to 300 mg/m², b.i.d.; with CsA co-treatment dose increased to 600 mg/m² b.i.d. 3. Measurement of MPA concentrations is strongly advised to optimise MMF therapy.
	Rationale for Strength of Evidence In this retrospective study, Filler et al. (2000; Charité Berlin) compared in paediatric kidney transplant patients the influence of the type of CNI given in combination with MMF on the resulting exposure to MPA. The MPA AUC achieved with MMF dosing did not differ between TAC and CsA co-treated patients, but the dose required to achieve therapeutic exposure was significantly lower in patients receiving concomitant TAC compared with CsA. The reason for the difference remained unknown at the time. However, as could be shown later, the difference is due to an interaction of CsA with MPA's enterohepatic recirculation and has been confirmed in later studies in paediatric as well as adult patients across all transplant types.			

Key Evidence				
Literature Reference*	**Study Design**	**Formulation/ Dosing**	**Demographics (number of patients; gender; age; other details)**	**Key Findings**
Hoecker et al. 2011	Subgroup analysis of FDCC trial, a 12-month, prospective, randomised study, comparing fixed-dose (FD) with concentration-controlled (CC) MMF dosing in paediatric and adult renal Tx recipients. Paediatric and adult patients treated on basis of the same immunosuppressive protocol. Concomitant therapy: CsA or TAC, steroids. MPA exposure estimated by abbreviated sampling in Week 4,6,12 post-Tx.	Formulation: n.a. MMF dose (first 30 days post-Tx) FD group: 600 mg/m² b.i.d. in children; 1 g b.i.d. in adults CC group: Initial dose as FD group, then adjusted to achieve target MPA AUC 30-60 h·mg/L	N = 62 paediatric (males/females = 32/30) and N = 839 adult (males/females = 523/316) renal Tx patients Age (mean ± SD) Paediatric 11.4 ± 4.5 yrs Adult 48.0 ± 13.3 yrs	1. MPA exposure significantly lower in **CsA**-treated paediatric and adult patients than in **TAC**-treated patients 2. Overall MMF **efficacy and tolerability** in paediatric patients under an equivalent MMF dosage and immunosuppressive protocol **comparable** with that in adults.
	Rationale for Strength of Evidence The prospectively planned FDCC trial by van Gelder et al. (2008) was the largest concentration-controlled trial in renal transplant patients with MMF to establish MPA exposure targets for optimal therapeutic benefit. Its design allowed for subgroup analyses, including the one presented by Hoecker et al. (2011) on the efficacy, safety and MPA plasma levels in paediatric (≥ 2 years) vs. adult kidney transplant patients. As the same immunosuppressive study protocol following Good Clinical Practice guidelines was used across all age groups, the analysis in 62 paediatric and 839 adult de novo patients allows for a robust comparison of efficacy, safety and pharmacokinetics in the two age groups (see also Key Findings provided above).			

Key Evidence				
Literature Reference*	**Study Design**	**Formulation/ Dosing**	**Demographics (number of patients; gender; age; other details)**	**Key Findings**
Weber et al. 1998	Open-label evaluation of the PK of MPA in paediatric in comparison to adult renal Tx recipients; early after tx; Concomitant administration of CsA, steroids MPA observations (free, total) 1 and 3 weeks post-Tx	Formulation: CellCept capsules 600 mg/m² b.i.d. (up to 2 g/day)	N= 18 (males/females = 10/8); first or second cadaveric or living-related donor. Age: 10.7 ± 0.72 (5.9–15.3) yrs, Weight: 29.3 ± 2.49 (16.0–50.3) kg BSA: 1.02 ± 0.06 (0.68–1.50) m²	1. **Concentration-time profiles of paediatric renal tx recipients** administered 600 mg/m² MMF b.i.d. **comparable to those in adults** on 1 g MMF b.i.d. after 3 weeks of surgery 2. **Free MPA fraction**, median 1.65% (range 0.40%- 13.8%) 3. **Renal impairment** and **decreased serum albumin** levels led to an **increase in free MPA** exposure.
Weber et al. 1999 (long-term follow-up of previously reported study, 3 and 6 months post-Tx)	Same as above	Same as above	Same as above	1. Doubling of exposure from 3-week to 3-month observation time point (**non-stationarity in total MPA**), **but not in free MPA**

Weber et al. 2002	Open-label longitudinal study of PKPD (free, total MPA) in 54 renal transplanted children concomitantly administered MMF, CsA, steroids. MPA observations (full profiles) on Days 7, 21, Months 3 and 6 post transplant.	Formulation: CellCept capsules 600 mg/m² b.i.d. up to 2 g/day	N = 54 (males/females = 33/21); Age median (range): 11.7 (range 2.2–17.8) yrs	1. Association between the **risk of acute rejection episodes and MPA exposure** ($AUC_{0\text{-}12h}$ predose levels). 2. By receiver operating characteristic analysis, an $AUC_{0\text{-}12h}$ of 33.8 h·mg/L in the initial phase post transplant had a diagnostic sensitivity of 75% and a diagnostic specificity of 64% for discrimination of patients with acute rejections. The relative risk of acute rejection was 41% with total MPA-$AUC_{0\text{-}12h}$ values below 33.8 h·mg/L compared with 14% with total MPA-$AUC_{0\text{-}12h}$ values above 33.8 h·mg/L. 3. The respective discrimination threshold for the MPA pre-dose concentration was 1.2 mg/L with a sensitivity of 83% and a specificity of 64%. 4. High free, but not total, MPA-$AUC_{0\text{-}12h}$ values were associated with an increased risk of the MMF-related side effects leukopenia and/or infections. Most of these adverse events were associated with **free MPA-$AUC_{0\text{-}12h}$** levels >0.4 h·mg/L.
	Rationale for Strength of Evidence By comparing, in the same study, the pharmacokinetics of MPA and of MPAG in paediatric and adult renal transplant recipients at equivalent doses based on BSA, Weber et al. (1998, 1999) provided, in a prospective study, definite evidence of comparable absorption and disposition of the MMF-derived products in children and adults. With this Weber et al. could show that 600 mg/m² b.i.d. MMF dosing in children leads to the same MPA exposure as 2 g b.i.d. in adults. Most importantly, Weber et al. concluded from their studies that the same MPA target exposure associated with a lower incidence of acute rejection episodes as established in adults (inter dose $AUC_{0\text{-}12}$ 30 h·mg/L) appeared also to be appropriate for children. Measurement of not only total, but also free concentrations in the two populations over the first three weeks after transplantation (Weber et al. 1998) and then also during 3-and 6-month follow-up (Weber et al. 1999), allowed to provide a mechanistic explanation for the previously empirically observed non-stationarity in the pharmacokinetics of MPA, which leads to gradual increases of total MPA over the first months of therapy in presence of unaltered dosing. Furthermore, the dependencies of unbound drug concentrations on degree of renal function and on albumin concentrations could be established. The studies by Weber et al. are unique in that they allow to compare the pharmacokinetics of MPA between the early and the late (more stable) phase after transplantation. The PK/PD relationship published by Weber et al. (2002) emerges from a continuation of the previously published prospective pharmacokinetic studies in renal transplant children (1998/1999). The interpretation of the risk of acute rejection episodes in paediatric patients on an immunosuppressive triple regimen (CsA, prednisone, MMF) in context with free and total MPA concentrations allowed to establish diagnostic exposure thresholds identifying patients at increased risk of acute rejection or of toxicity in the initial phase post transplant. The value of the information presented by Weber et al. (1998, 1999, 2002) ranks very high as definite information could be obtained in a difficult-to-study population including a relatively large cohort, studied in the early and late post-transplantation period. Thanks to the careful studies by Weber et al., MPA concentration characteristics after chronic dosing could well be defined and their peculiarities be traced back to underlying disposition characteristics. The dose-concentration relationship could then be expanded by inclusion of effects (desired, undesired) so that also clear concentration-effect relationships could be derived. Clearly, with this study Weber et al. have provided reference data for subsequent studies.			

Paediatric heart transplantation:

Table 4 Comparative Data: Paediatric Heart Transplantation (Literature References)

Key Evidence				
Literature Reference	**Study Design**	**Formulation/ Dosing**	**Demographics (number of patients; gender; age; other details)**	**Key Findings**
Dipchand et al. 2001a	Review of paediatric heart Tx database (Nov 1997-Oct 1988). Review relationship of serum trough MPA levels and dose; target trough level >3 µg/L (*sic*)	CellCept; crushed tablets	N = 44 (males/females = 27/17); Median age at Tx 2.7 yrs (7 days - 18.4 yrs).	**1. Higher MMF doses may be required by children at younger ages and in the early period after tx.** 2. Dosing by body surface area may be advantageous. 3. Therapeutic drug monitoring of MPA may be required for optimal dosing.
	Rationale for Strength of Evidence Dipchand et al. (2001a) present the cross-sectional results from a review of data in the paediatric heart transplant database at the Children's Hospital in Denver Colorado (observation period approximately one year). The analysis was based on a sizeable number of patients (n=44), but limited number of trough MPA levels (n=128). From the majority of patients more than one sample could be obtained. Given the paucity of information from paediatric heart transplant patients, the results from this analysis are very valuable and important conclusions could be drawn, not only on pharmacokinetics, but also on the relationship of MPA concentrations and rejection episodes. With a median age at transplant of 2.7 yrs, many very young patients were apparently included in the study. This study was the first in the literature to report MMF dose and resultant MPA levels in heart-transplanted children with a wide span of ages.			

Key Evidence				
Literature Reference	**Study Design**	**Formulation/ Dosing**	**Demographics (number of patients; gender; age; other details)**	**Key Findings**
Gajarski et al. 2004	Retrospective analysis of medical records of paediatric and young adult cardiac Tx patients treated with MMF in combination with a CNI (TAC, CsA).	Formulation: n.a. Paediatric dosing: 1200 mg/m² (≤3 g) per day	n=16 children, n=10 adults; Age 15.4 ± 9.5 yrs (1 month - 33 yrs).	**1. No correlation of MMF dose with MPA/MPAG levels; standard MMF dosing fails to consistently achieve "therapeutic" MPA concentrations.** 2. Concentration- rather than dose-driven management is more prudent strategy when using MMF. 3. Plasma levels ≥ 2.5 mg/L are associated with lower biopsy grades.
	Rationale for Strength of Evidence In a retrospective review of patient records, Gajarski et al. (2004) addressed the frequency with which standard dosing could achieve therapeutic plasma concentrations in paediatric and adult heart transplant patients, with a view of determining a threshold MPA concentration which minimises rejection risk. Trough levels only served as measure of achieved exposure, but multiple levels per subject were available. By including paediatric and adult patients in the analysis, a comparison across these age groups was possible. The authors were well aware of limitations and bias, which could be introduced by their analysis. To mitigate these, they used various modalities for analyzing their database. Hence, the conclusions on no statistical difference in MPA exposure at therapeutic levels between paediatric and young adult groups, on a trend to under dosing with recommended dosing regimens, and on the proposed threshold trough level of 2.5 mg/L for lower rejection risk, appear to be robust.			

CNI=calcineurin inhibitor; CsA=ciclosporin A; MMF=mycophenolate mofetil; MPA=mycophenolic acid; MPAG=mycophenolic acid phenolic glucuronide; n.a.=not available; TAC=tacrolimus; Tx = transplant(ation); yrs=years.

Paediatric liver transplantation:

Table 5 Comparative Data: Paediatric Liver Transplantation (Roche Study Report)

Study / Reference*	**Study Design**	**Formulation/ Dosing**	**Demographics (number of patients; gender; age; other details)**	**Key Findings**
Lobritto et al. 2007 Study PA16497 (Roche Report No. 1019844)	Open-label study in paediatric patients with liver Tx ≥6 month's prior to study entry. All patients on stable CsA ≥2 days prior to plasma sampling.	Formulation n.a. MMF dose median 125 mg (mean±SD 138±52.2 mg); corresponding to 270 mg/m² (285±81.1 mg/m²), 12.6 mg/kg (12.9±3.32 mg/kg)	N=8 patients (males/females=3/5); median age 16 (range 9–60) months; median body weight 10.5 kg (mean ± SD 10.6 ± 2.1 kg); median BSA 0.465 m² (0.476 ± 0.064 m²). Time since Tx: ≥6 months.	1. **Rationale for dose recommendation in paediatric liver Tx patients with concomitant CsA treatment.** 2. In combination with CsA, MMF dosing of 740 mg/m² twice daily achieves MPA exposures in paediatric liver Tx patients similar to those observed in adult liver Tx recipients, 58 h·mg/L during the late post-Tx period (>6 months) and 29 h·mg/L in the immediate post-Tx period.
Assessment of Relevance A single open-label, multi-centre uncontrolled study in paediatric liver allograft recipients (Study PA16497) was conducted in Roche's paediatric liver transplantation program. The study was to estimate the MMF dose required in this population in presence of CsA and corticosteroids for prophylaxis of acute organ rejection. An exposure was targeted in the study that would provide an MPA exposure in paediatric patients that was comparable to that achieved in adult liver transplant patients receiving the approved dose of MMF in Study MYCS2646 (58 h µg/mL in the late, 29 h µg/mL in the immediate post-transplant period. The first part of the study was designed to estimate a dose that would provide the target MPA exposure in the late post-transplant period; the second confirmatory part of the study was to provide the pharmacokinetics, efficacy, and safety profiles of the proposed dose in the immediate post-transplant period - but this second part was not conducted due to an early termination of the study (difficulties in recruitment).				

BSA=body surface area; CsA=ciclosporin A; MMF=mycophenolate mofetil; MPA=mycophenolic acid; Tx=transplant(ation); yrs=years.

Table 6 Comparative Data: Paediatric Liver Transplantation (Literature References)

Key Evidence				
Literature Reference*	**Study Design**	**Formulation/ Dosing**	**Demographics (number of patients; gender; age; other details)**	**Key Findings**
Brown et al. 2002	21 stable paediatric liver Tx patients (9 females, 12 males) on oral MMF therapy combined with either low-dose TAC (n=11) or low-dose CsA (n=10).	n.a.	Age median (range) 9.5 (2.1–15.5 yrs); weight 9.4–80 kg. Median (range) time since Tx 4.7 (1.3–11.4) yrs.	1. **Co-medication with CsA demanded higher MMF doses** to achieve equivalent trough levels than with TAC. 2. Trough levels were closely correlated with AUC. 3. Wide inter-individual variability in MPA pharmacokinetics showed need for therapeutic drug monitoring.
	Rationale for Strength of Evidence The publication by Brown et al. (2002) was the first to report on the absorption and disposition characteristics of MPA/MPAG in paediatric liver transplant patients (stable phase after transplantation). To find the right dose, initially low doses of MMF were increased if well tolerated (up to 1 g twice daily) or reduced if side effects emerged. Concomitantly administered immunosuppressants were a CNI (CsA or TAC) and steroids. The analysis of this prospective study is based on 7-h concentration-time profiles and is of high quality. MPA and MPAG concentrations were determined by a specific HPLC method. Findings from Brown et al. (2002) served as reference for later studies in the same paediatric population as they clarified the key aspects of MPA pharmacokinetics in liver transplanted children; they also addressed the effects of covariates on MPA and MPAG pharmacokinetics and the influence of the type of co-administered CNI on MPA disposition. The number of children in the study may seem limited, but was adequate to define the relevant determinants of MPA absorption and disposition.			

Key Evidence				
Literature Reference*	**Study Design**	**Formulation/ Dosing**	**Demographics (number of patients; gender; age; other details)**	**Key Findings**
Barau et al. 2012 (Barau et al. 2011)	Paediatric liver Tx patients received oral MMF therapy combined with either TAC (n=23) or CsA (n=5). Intensive sampling to determine population parameters.	Formulation: n.a. (partly oral suspension) MMF starting dose: median 380 mg/m² (13.0 mg/kg), range 186-594 mg/m² - b.i.d. MPA-guided dose adjustment to achieve MPA $AUC_{0\text{-}12h}$ between 30-60 h·mg/L	N = 28 patients (males/females=14/14) Age range 1.1–18 (median 8.65) yrs Weight 9.3–63.2 kg BSA 0.44–1.69 m² Time since Tx: median (range) 17.2 (0.2–188.5) months.	From Barau et al. 2012 (full dataset) 1. **Time after Tx** (≤ vs. >6 months) and **age** affect MPA PK in paediatric liver Tx patients. 2. MPA exposure helps to optimise paediatric patient care and can be determined by a simple sampling procedure. From Barau et al. 2011 (smaller, overlapping dataset) 1. MMF **dosage** had to be increased in all but 1 patient to reach at least 30 h·mg/L exposure. An initial MMF dose of 600 mg/m² b.i.d. is required for paediatric liver tx recipients when MMF is administered together with TAC to achieve the target MPA $AUC_{0\text{-}12h}$ of 30 h·mg/L. 2. For 2 patients with co-administered **rifampicin** in addition to MMF, MPA $AUC_{0\text{-}12h}$ remained low despite a 2-fold increase in the MMF dose.
	Rationale for Strength of Evidence The prospective studies by Barau et al., published first with a reduced and later with an enlarged data set, address several therapy-relevant pharmacokinetic aspects of MMF dosing in paediatric liver transplant patients. Not only were total and also free (protein-unbound) concentrations from an extensive sampling strategy available, but the authors also applied population pharmacokinetic modelling to evaluate factors (covariates) possibly contributing to the overall high variability seen in MPA concentrations. Quantification of MPA and MPAG levels and protein binding determinations were based on state-of-the-art methods (validated HPLC methods, unbound fraction determined by ultrafiltration) and results can therefore be judged as reliable. The applied mathematical model was appropriately validated using an external validation data set. Both, early and late (stable) transplant periods were covered by their paediatric population and allowed to elucidate differences between these periods and possible mechanistic explanations for them. The data could be interrogated to propose a limited sampling strategy allowing to estimate the inter-dosing AUC based on a small number of appropriately timed samples. For unexplained reasons (lack of or reduced enterohepatic recirculation in liver transplant patients?), no different exposure was seen in TAC and CsA-co-treated children.			

Key Evidence				
Literature Reference*	**Study Design**	**Formulation/ Dosing**	**Demographics (number of patients; gender; age; other details)**	**Key Findings**
Ueno et al. 2020	5 paediatric liver Tx patients on oral MMF therapy combined with TAC and steroids. MMF dose adjustment to reach target trough MPA 2 mg/L. Duration of observation: 17 (6-30) months	Formulation: n.a. Mean (range) initial MMF dose: 32 (23-53) mg/kg, 770 (570-960) mg/m²/day	Mean (range) Age at Tx 8 (3–10) months; Weight 7.6 (4.7–10.7 kg); BSA 0.35 (0.26–0.39) m²	Mean final MMF dose for 2 mg/L target trough concentration was 1200 mg/m²/day or 50 mg/kg/day
	Rationale for Strength of Evidence The study by Ueno et al. (2020) is of high value and importance - not so because of a large patient population, extensive sampling, or broad focus, but because a very young patient population (5 infants after living-donor liver transplantation; age at transplant 3-10 months) was studied. This study allowed to verify (and confirm) observations by several authors that dose requirements are higher in the very young population than in older paediatric patients. These conclusions were drawn after adjusting the mean initial dose of 32 mg/kg by targeting a trough level of ≥2 mg/L - required mean final dose was 66 (range 47-106) mg/kg/day, corresponding to 1430 (1280-1920) kg/m2/day, for a trough level of 2.7 (2.2-3.5) mg/L.			

Supportive Evidence				
Literature Reference*	Study Design	Formulation/ Dosing	Demographics (number of patients; gender; age; other details)	Key Findings
Parant et al. 2009	Prospective open-label study in paediatric patients with liver Tx ≥3 months prior to study enrolment; TAC co-administration	Formulation CellCept MMF dose median 431 (range 189-833) mg/m²/day	N = 20 patients (males/females=11/9); Median (range) Age 12 (1–18) yrs; Weight 31.4 (8.2–61) kg; Paediatric/adult donors: 12/8; Time since Tx: ≥3 months Analytics: EMIT	1. **Donor characteristics** had an influence on MPA exposure in the youngest children. 2. To achieve a target MPA-AUC of 45 h·mg/L, MMF doses required were 400-800 mg/m²/day when combined with TAC; young children receiving livers from paediatric donors required doses of 600-1000 mg/m²/day
	Rationale for Strength of Evidence The prospective study by Parant et al. (2009) in stable paediatric liver transplant children had an interesting focus, namely reasons for the high variability in MPA's pharmacokinetics with a view of factors relating to recipient age and donor characteristics (paediatric vs. adult). The study uncovered that there were differences between recipients of paediatric and adult livers in age dependence of dose requirements to achieve recommended MPA exposure. In the study repeat profiles from children (up to 4 repeats/individual) were available. Unfortunately, no evaluation or information in the study description is given on the results from these repeated measurements - a missed opportunity. The presented study has several limitations and results require confirmation in a larger cohort. The low starting dose of 20 mg/kg led to underexposure in a majority of patients and had been found particularly pronounced in the younger patients. This was obviously a surprise to the authors, but based on the standard dosing recommendation for children actually had to be expected. The assignment to one of two age categories in the data analysis, young and older paediatric patients, with a boundary value of 10 years, is artificial and conclusions for the "young" category may not apply to all ages below 10 years. For quantification of MPA in the study, the non-specific EMIT assay was applied. Furthermore, the AUC exposure measure in the study was estimated based on an abbreviated profile (4 data points determined up to 6 h post administration). The use of this reduced AUC to explore single time point measures, which could equally well predict the full AUC, is not appropriate and conclusions by the study authors relating to this need clearly confirmation.			

Supportive Evidence				
Literature Reference*	Study Design	Formulation/ Dosing	Demographics (number of patients; gender; age; other details)	Key Findings
Tannuri et al. 2007	MMF, initiation in 11 paediatric liver Tx patients after renal impairment induced by CNI; reduction of CNI dose to 50%.	Formulation: n.a. MMF dose initially 20 mg/kg/day, increased to 40 mg/kg/day within 2-week interval	N=11 children (males/females=5/6) with liver Tx and renal dysfunction; time post- Tx 1.3–12.5 yrs Age range: 3–15 yrs Weight range: 14–55 kg	1. 40 mg/kg/day **MMF promoted prolonged improvement in renal function without changing liver function.** 2. Early introduction of MMF benefits patients with minimal renal dysfunction and prevents irreversible renal damage.
	Rationale for Strength of Evidence Tannuri et al. (2007) investigated retrospectively a special situation, namely initiation of MMF therapy and reduction of CNI doses in paediatric liver transplant patients with renal impairment (secondary to prolonged use of CsA or TAC). At the time of introduction of MMF, the 11 transplant recipients were all in the stable post-transplant period and ranged in age from 3 to 15 yrs. Although the patients were not monitored for levels of MPA, the study contributes importantly to an assessment of the beneficial kidney-sparing effects of MMF in paediatric liver transplant patients.			

Supportive Evidence				
Literature Reference*	Study Design	Formulation/ Dosing	Demographics (number of patients; gender; age; other details)	Key Findings
Attard et al. 2008	Validation of limited sampling strategy in paediatric liver Tx recipients by measurement of serial 0-8 h MPA plasma concentrations from an open-label multi-centre study.	Formulation: n.a. MMF (mean [SEM]): Center Baltimore: TAC co-med: 219 (40) mg/day Center London: TAC co-med: 285 (45) mg/day CsA co-med: 548 (71) mg/day	N = 41 children from two centres; mean (SEM). Center Baltimore: males/females = 8/12, median Age 4.0 (0.5–17.2) yrs Weight: 26.7 (4.3) kg BSA: 0.9 (0.1) m² MPA analytics: HPLC Center London: males/females = 10/11, median Age 6.2 (1.2–16.5) yrs Weight: 33.6 (4.2) kg Height: 128 (5.5) cm BSA: 1.1 (0.1) m² MPA analytics: EMIT	1. Higher required MMF doses when combined with **TAC** than with **CsA** 2. The **very young patients** (age <1 yr) achieved lower overall plasma MPA AUC
	Rationale for Strength of Evidence Two different data sets were available to Attard et al. (2008) for an evaluation of the value of a limited sampling strategy, allowing to estimate, in paediatric liver transplant patients treated with MMF, MPA exposure using relevant and feasible metrics. Two transplant centres contributed concentration-time profiles covering 8 h (of the 12-h dosing interval?). As one of the centres included patients co-treated with TAC or CsA, observed differences in MPA exposure between groups with a different CNI could reliably be assessed. There were important limitations in the study to judge the observed pharmacokinetic characteristics of MPA. Time of sample collection after transplantation (early, late) was not specified. Dosing applied was described as "conventional drug dosing practices", but there is uncertainty around dosing strategies. Mean doses administered are given in mg/day and it is not clear to what dose relative to BSA they relate to. Furthermore, there were differences between the centres in doses administered (despite no apparent differences in height, weight, BSA between patients), and in the analytical methods employed for MPA quantification (EMIT vs HPLC). Confusingly, although MPA AUCs were apparently calculated, the values listed for them are actually in units of concentrations and a "median MPA level" was given.			

AUC=area under the concentration-time curve; AUC_{0-12h}=area under the concentration-time curve from time 0 h to 12 h; BSA=body surface area; CNI=calcineurin inhibitor; CsA=ciclosporin A; EMIT=enzyme multiplied immunoassay technique; HPLC=High Performance Liquid Chromatography; MMF=mycophenolate mofetil; MPA=mycophenolic acid; n.a.=not available; SEM=standard error of mean; SD=standard deviation; TAC=tacrolimus; Tx=transplant(ation); vs.=versus; yrs=years.

The paediatric extrapolation approach used is based primarily on PK-comparison with the adult reference population, under the assumption that a similar exposure produces a similar efficacy. This follows the recommendation in the guideline on the role of pharmacokinetics in the development of medicinal products

in the paediatric population (EMEA/CHMP/EWP/147013/2004). The approach is supported by one paediatric clinical study in liver transplant patients, study PA16497, previously submitted paediatric clinical studies in renal transplant patients and by published studies in the literature. All submitted clinical studies of MAH, except for the study PA16497 in paediatric liver transplant recipients, have previously been assessed.

2.3.2. Pharmacokinetics

ADME

Similarity in MPA absorption and disposition between paediatric and adult transplant Recipients

The key characteristics of MPA absorption and disposition observed in adult transplant recipients are also seen in paediatric patients (Filler et al. 2008; Barau et al. 2012). Concentration-time profiles of paediatric renal transplant recipients receiving MMF at a dose of 600 mg/m2 twice daily in combination with CsA were comparable to those in adults on 1 g MMF twice daily (again with concomitant CsA) in the first 3 weeks after transplantation (Weber et al. 1998; Filler et al. 2004b). Similar to adults, children rapidly absorb MMF and form the active compound, MPA, which peaks at 45 minutes after oral intake. MPA is highly bound to albumin. Albumin binds many drugs, preferentially drugs with acidic functionalities such as MPA. Its reference values change with age. Recently Sethi et al. (2016) characterized the ontogeny of albumin by determining albumin concentration in age cohorts with sufficient data points and in relevant age categories. Levels of albumin progressively increase in the plasma during maturation. Increases from one age group to the next were modest, such that no one group was significantly different from the next. However, values from infants up to 3 years were significantly lower than for adults. Free fractions of MPA in plasma were no different in paediatric (1.7%) than in adult (1.9%) transplant patients when serum albumin concentrations were in the physiological range (Weber et al. 1998). These binding values in transplanted children were confirmed by studies in paediatric patients after haematopoietic stem cell transplantation (HSCT), where a difference between boys (1.7%) and girls (2.6%) was found according to Zhang et al. (2016).

Similar to adults, there is a second peak in concentrations because of enterohepatic recirculation (EHC) of the main metabolite MPAG. Similar to adults, when combining immunosuppressant drugs in a therapeutic strategy, CsA interferes with MPA disposition (EHC) and decreases MPA plasma levels (Filler et al. 2000; Dhawan 2011). Absence of such an interaction with TAC has equally been found in children and adults (Filler et al. 2004b). Similar to adults there is a non-stationarity seen in the exposure to MPA when comparing values in the immediate post-transplantation phase (≤6 months) with values in the stable post-transplantation period (>6 months) (Weber et al. 1999).

Drug distribution depends to a great extent on body composition. The body composition of neonates and young infants differs from that of adults: they have more extracellular and total body water, which may lead to lower plasma levels of drugs when they are administered on a weight basis (Siber et al. 1975).

MPA concentrations critically depend on the liver's capacity for glucuronidation and for EHC. Weight-corrected doses for drugs eliminated by glucuronidation generally are similar in children compared to those in adults (Anderson 2010) because enzymatic activity of uridine diphosphate glucuronosyltransferase (UGT) differs significantly less between children and adults than what is observed for key cytochrome-P450 isozymes (Anderson 2010).

However, this may not apply to very young children. UGT activity in neonates is deficient at birth and increases significantly during the first years of life to reach adult levels by 2–4 years of age (Miyagi and Collier 2007; Anderson 2010). In early neonatal life, glucuronidation is substantially lower (50%–70% of

adult values) (Loebstein and Koren 1998). The pharmacological consequences of reduced glucuronide formation in neonates has been shown with acetaminophen, a drug also extensively conjugated by phenolic glucuronidation in adults. In case of acetaminophen, increased sulfation in neonates could make up for the reduced glucuronidation pathway (Levy et al. 1975; Miller et al. 1976). Older children appear to have slightly increased UGT activity compared with adult levels.

UGT1A9 is amongst the most abundantly expressed UGTs in neonatal liver. Its activity develops in an age-dependent manner (Miyagi et al. 2012) with zero activity at birth and increasing to its maximum by 4 months of age. Activity does not differ between genders. Enzyme activity is correlated with expression. Expression of UGT1A9 correlated strongly with age, but only in children younger than 1 year. Adult expression was reached by 3.8 months; maximum expression was reached by 12 months of age. After 1 year of age, intrinsic clearance of a UGT1A9 model substrate (4-methylumbelliferone) slowly decreases to reach adult levels at approximately 20 years of age

The foetal liver is capable of enterohepatically recycling glucuronides. The activity of β-glucuronidase in the liver is highest in the neonatal liver and decreases to steady-state adult levels by 4 months of age (Miyagi and Collier 2007). Hence, the balance of glucuronide metabolism and disposition shifts very early in the neonate from cleavage and recirculation to conjugation and clearance.

PK in adult reference population and in paediatric renal transplant population

Exposure target in adult reference population – kidney transplantation (Study MYC058)

A relationship between exposure to MPA and prevention of rejection was established in adult kidney transplant patients to determine the appropriate dosing of MMF (Study MYC058). In this concentration-controlled study, 150 patients were dosed with MMF to achieve three different target exposure levels; patients were randomly assigned 1:1:1 to either a low (16.1 h·mg/L), intermediate (32.2 h·mg/L) or high (60.6 h·mg/L) exposure. Multiple MPA and 7-O-MPA glucuronide (MPAG) concentration profiles were determined early and late after transplantation. Patient MMF dosage was individualised based on the observed MPA area under the plasma concentration-time curve from time 0 h to time 12 h ($AUC_{0\text{-}12h}$) to achieve these target levels. The primary efficacy comparison (biopsy-proven rejection vs. successful completion of study with no biopsy-proven rejection) was analysed using logistic regression for the variable median ln(MPA $AUC_{0\text{-}12h}$). This analysis led to the conclusion that an MPA $AUC_{0\text{-}12h}$ of 27.2 h·mg/L as the target value in the early post-transplant period provided an optimal benefit in the prevention of rejection with an acceptable safety profile.

The target exposure ($AUC_{0\text{-}12h}$) of 27.2 h·μg/mL established in Study MYC058 was used to select the appropriate dose in Roche's renal transplant program and also guided dosing in paediatric liver transplant patients.

Comparison of pharmacokinetics across transplant indications in adults

A comparison of PK parameters of MPA in adult renal, cardiac, and hepatic transplant patients at various times after transplantation as derived from studies conducted by Roche is shown in **Table 7** below. Whereas T_{max} and C_{max} reflect MMF to MPA conversion and absorption characteristics, the inter-dosing interval $AUC_{0\text{-}12h}$ is influenced by, besides the extent of absorption, the MPA disposition and EHC. The comparison shows a high degree of similarity in absorption and disposition behaviour of MPA during early and late phases after transplantation in the three groups of patients. In the early post-transplant period (<40 days post transplant) renal, cardiac and hepatic transplant patients all had mean AUCs approximately 20%–40% lower and mean C_{max} values approximately 32%–44% lower compared to the late transplant period (3 to 6 months post-transplant).

Table 7 Comparative Pharmacokinetic Parameters of Mycophenolic Acid in Adult Renal, Cardiac, and Hepatic Transplant Patients

Time after transplantation	Dose / Route	T_{max} (h)	C_{max} (mg/L)	Interdosing Interval AUC_{0-12h} (h•mg/L)
Renal Transplant Patients (b.i.d. dosing)				
5 days	1.0 g b.i.d. / IV	1.58 (±0.46) (n=31)	12.0 (±3.82) (n=31)	40.8 (±11.4) (n=31)
6 days	1.0 g b.i.d. / oral	1.33 (±1.05) (n=31)	10.7 (±4.83) (n=31)	32.9 (±15.0) (n=31)
Early (<40 days)	1.0 g b.i.d. / oral	1.31 (±0.76) (n=25)	8.16 (±4.50) (n=25)	27.3 (±10.9) (n=25)
Early (<40 days)	1.5 g b.i.d. / oral	1.21 (±0.81) (n=27)	13.5 (±8.18) (n=27)	38.4 (±15.4) (n=27)
Late (>3 months)	1.5 g b.i.d. / oral	0.90 (±0.24) (n=23)	24.1 (±12.1) (n=23)	65.3 (±35.4) (n=23)
Cardiac Transplant Patients (b.i.d. dosing)				
Early (Day before discharge)	1.5 g b.i.d. / oral	1.8 (±1.3) (n=11)	11.5 (±6.8) (n=11)	43.3 (±20.8) (n=11)
Late (>6 months)	1.5 g b.i.d. / oral	1.1 (±0.7) (n=52)	20.0 (±9.4) (n=52)	54.1[a] (±20.4) (n=49)
Hepatic Transplant Patients (b.i.d. dosing)				
4 to 9 days	1 b.i.d. / IV	1.50 (±0.517) (n=22)	17.0 (±12.7) (n=22)	34.0 (±17.4) (n=22)
Early (5 to 8 days)	1.5 b.i.d. / oral	1.15 (±0.432) (n=20)	13.1 (±6.76) (n=20	29.2 (±11.9) (n=20)
Late (>6 months)	1.5 b.i.d. / oral	1.54 (±0.51) (n=6)	19.3 (±11.7) (n=6)	49.3 (±14.8) (n=6)

AUC_{0-12h}=area under the concentration-time curve from time 0 h to 12 h; b.i.d.=twice a day; C_{max}=maximum concentration; IV=intravenous; T_{max}=time to maximum concentration.

[a] AUC_{0-12h} value quoted is extrapolated from samples collected over 4 hours.

Paediatric kidney transplantation

The paediatric program consisted of two paediatric studies, an initial dose-ranging pilot study (MYC2190) and a single pivotal study (MYCS2675), enrolling a total of 140 paediatric renal transplant patients (defined as an individual between 3 months and 18 years of age, inclusive); all patients in these two studies received MMF. Study MYCS2675 provided the basis for the labelled dose recommendation of 600 mg/m2 for the prophylaxis of rejection in paediatric renal allograft patients. The development of MMF for paediatric use was based extensively on the balanced risk-benefit profile previously established in adults.

Dose-ranging Study MYC2190

The pilot paediatric study (Study MYC2190) using CellCept capsules was conducted to determine the PK of MPA and MPAG in patients aged 3 months through 18 years of age and to determine the dose which would deliver in this paediatric patient population a target MPA exposure of AUC_{0-12h} of 27.2 μg·h/mL. This target exposure had previously been derived from the PK/PD Study MYC058 in adult kidney transplant patients. In that PK/PD study this exposure of 27.2 μg·h/mL had been computed to be associated, on average, with a 1 g twice daily (b.i.d) dose for adults in the early post-transplant period — a dose which had been established as safe and efficacious in the primary adult renal transplant trials.

The dose selected after evaluating the results from Study MYC2190 was then subsequently tested in the paediatric pivotal Study MYCS2675.

Study Summary

The patients received 15, 23, or 30 mg/kg CellCept b.i.d. for the prevention of renal allograft rejection. In this study, 23 mg/kg b.i.d. most closely achieved the adult target MPA AUC_{0-12h} of 27.2 μg·h/mL. The study was originally intended to last for 3 years. However, the study was terminated early by the Sponsor, because, based on PK data collected in this paediatric population, it was possible to make more specific dosing recommendations, which were then implemented in a follow-on study (2190v2). At study closure, most patients had received MMF for 1-2 years. Most patients then enrolled into Study 2190v2 in which they could continue on MMF at a dosage of 23 mg/kg b.i.d. until they had completed 3 years on MMF.

Pharmacokinetic results

For the 11 patients who received 23 mg/kg, the mean MPA AUC_{0-12h} was 28.1±11.9 μg·h/mL and maximum concentration (Cmax; n=12) was 8.57±4.62 μg/mL on Day 14. Because of the substantial inter-subject variability, additional analyses were performed which indicated that calculating doses based on estimated body surface area (BSA) (mg/m2) reduced the coefficient of variation by about 10% (Study MYC2190). **Table 8** was then constructed from linear regression of MPA AUC_{0-12h} versus dose from MYC2190 data and adult data. The dose which was predicted to provide a MPA AUC_{0-12h} closest to the desired 27.2 μg·h/mL was 600 mg/m2.

Table 8 Projected MPA AUC to CellCept Dose from Adult and Paediatric Data

CellCept dose (mg/m^2)	Projected MPA AUC_{0-12h} (μg*h/mL) [a]
450	20.7
500	23.2
550	25.7
600	28.2
650	30.8
700	33.3

AUC=area under the plasma concentration-time curve; AUC_{0-12h}=area under the plasma concentration-time curve from time 0 h to time 12 h; MPA=mycophenolic acid.

[a] from adult data (Studies MYC024/GER, ICM 1753, MYC1866 and NSK024) and paediatric data (Study MYC2190, Day 21)

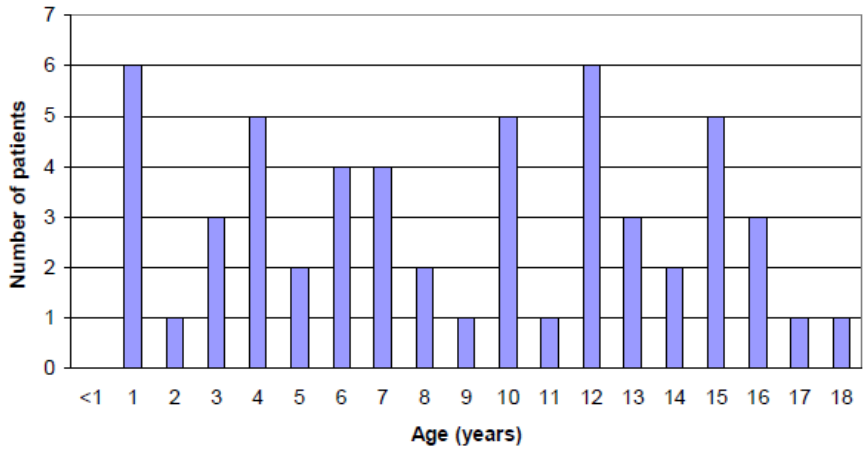
Pivotal Study MYCS2675

Study MYCS2675 is the pivotal study of the renal paediatric program as it provides the majority of the safety, PK, and efficacy data.

Study Summary

Study MYCS2675 was a single-arm, open-label, safety, and PK study in 100 paediatric patients receiving a first or second renal allograft. Pharmacokinetic sampling was performed in a subset of 55 of the 100 paediatric patients (age range 1-18 years; the age distribution is shown in **Figure 1**. Results from three age groups were compared (3 months to <6 years, 6 to <12 years, and 12 to 18 years). Each patient received MMF suspension dosed at 600 mg/m2 b.i.d. (body surface area (BSA)) up to a maximum of 1 g b.i.d., with ciclosporin and corticosteroids administered as per local centre practice. After nine months in the study, patients with a BSA of at least 1.25 m2 who were able to swallow capsules and preferred the convenience of capsules to that of suspension, could elect to receive the capsule formulation of MMF.

Figure 1 Distribution of Age of the Number of Paediatric Patients in Study MYCS2675 for which Full Pharmacokinetic Profiles Were Determined



Blood sampling to determine full PK profiles of MPA and MPAG were collected at Day 7, Month 3, and Month 9 in a subset of 55 of the 100 paediatric patients in Study MYCS2675. The PK-subset was generally representative of the larger sample. Allograft biopsies and treatment of acute rejection were monitored to allow determination of rejection-related endpoints through six months post-transplant. Safety parameters included deaths, malignancies, opportunistic infections, and other adverse events (AEs).

Pharmacokinetic results

Pharmacokinetic parameters for MPA and 7-O-mycophenolic acid glucuronide (MPAG) stratified by age and time after transplantation in the pharmacokinetically characterized patients are given in **Table 9** and **Table 10**, respectively.

A 1.9-fold increase in mean dose-adjusted MPA AUC_{0-12h} was observed in the later post-transplant period (Day 7 vs. Month 3 post transplant) for all patients. The increase was 1.11-fold between Months 3 and 9.

MMF suspension given to patients 1 to 18 years of age produced no statistically significant differences ($p < 0.05$) in mean MPA plasma concentrations or in mean computed parameters (e.g., AUC_{0-12h}) between the three age groups, with one exception. The dose-adjusted maximum concentration (C_{max}) at Month 9 in the oldest group (12-18 years) was lower than in children of younger age. This observation is considered to be of minor relevance as the therapeutic effect is associated with the average exposure during a dosing interval (area under the plasma concentration-time curve from time 0 h to time 12 h [AUC_{0-12h}]) rather than with maximum concentrations. Importantly, the mean dose-adjusted MPA AUC_{0-12h} for all patients was similar to the desired target MPA AUC_{0-12h} (27.2 hmg/L). There was a statistically

significant difference in mean dose-adjusted MPAG AUC_{0-12h} across the age groups at all time points, with values increasing from the youngest to the oldest group, see **Table 10**.

Six of the patients in Study MYCS2675 studied for PK parameters were between the age of 1-2 years. A listing of their individual demographic details is given in **Table 11** along with calculated PK parameters. Although few in number, the values for mean calculated MPA PK parameters in the <2-year age group were similar to those of the other age groups (**Table 10**). The mean MPA AUC_{0-12h} was numerically lower (22.5 h mg/L) than the target mean MPA AUC_{0-12h}, with a wide degree of variability (95% CI: 17.2-27.8 h mg/L), due to the small sample size. **Figure 2** shows that dose-adjusted MPA AUC_{0-12h} was not affected by age in the range of 1 18 years. Patients in the <2-year subgroup had the lowest mean dose-adjusted MPAG AUC_{0-12h} at the earlier time points, but by Month 9 the value was similar to that observed for the <6-year group.

A retrospective demographic analysis of patients <2 years old across the paediatric studies performed in renal transplant patients revealed one additional patient in this low age group who had been included in Study MYC2190. His data are included in **Table 11**. The BSA of this child aged 1 year, 8 months at enrolment was much lower than the one in the patients of even younger age from Study MYCS2675. Likewise, his dose-adjusted AUC_{0-12h} was substantially lower than what had been found in the six subjects in Study MYCS2675.

Table 9 Mean Computed MPA PK Parameters by Age and Time After Transplantation

Age Group (n)	T_{max} hr	Adjusted C_{max} µg/ml[A]	Adjusted AUC_{0-12} µg•h/ml (CI)[A]
Day 7			
< 6 y (17)	1.63 ± 2.85	13.2 ± 7.16	27.4 ± 9.54 (22.8 – 31.9)
6 – < 12 y (16)	0.940 ± 0.546	13.1 ± 6.30	33.2 ± 12.1 (27.3 – 39.2)
12 – 18 y (21)	1.16 ± 0.830	11.7 ± 10.7	26.3 ± 9.14 (22.3 – 30.3)[D]
p-value[B]	–	–	–
< 2 y[C] (6)	*3.03 ± 4.70*	*10.3 ± 5.80*	*22.5 ± 6.68 (17.2 –27.8)*
Month 3			
< 6 y (15)	0.989 ± 0.511	22.7 ± 10.1	49.7 ± 18.2
6 – < 12 y (14)[E]	1.21 ± 0.532	27.8 ± 14.3	61.9 ± 19.6
12 – 18 y (17)	0.978 ± 0.484	17.9 ± 9.57	53.6 ± 20.2[F]
p-value[B]	–	–	–
< 2 y[C] (4)	*0.725 ± 0.276*	*23.8 ± 13.4*	*47.4 ± 14.7*
Month 9			
< 6 y (12)	0.869 ± 0.479	30.4 ± 9.16	60.9 ± 10.7
6 – < 12 y (11)	1.12 ± 0.462	29.2 ± 12.6	66.8 ± 21.2
12 – 18 y (14)	1.069 ± 0.518	18.1 ± 7.29	56.7 ± 14.0
p-value[B]	–	0.004	–
< 2 y[C] (4)	*0.604 ± 0.208*	*25.6 ± 4.25*	*55.8 ± 11.6*

[A] C_{max} and AUC_{0-12} are adjusted to a dose of 600 mg/m^2; 95% confidence intervals (CI) for AUC_{0-12} day 7 only.
[B] p-value represents the combined p-value for the three major age groups, and is noted only if significant ($p < 0.05$).
[C] The < 2 year group is a subset of the < 6 year group; no statistical comparisons were made.
[D] n = 20
[E] Data for one patient was unavailable due to sampling error.
[F] n = 16

Table 10 Mean Computed MPAG PK Parameters by Age and Time After Transplantation

Sampling Time (n)		T_{max} hr	Adjusted C_{max} µg/ml[A]	Adjusted AUC_{0-12} µg•h/ml[A]
Day 7				
< 6 y	(17)	2.41 ± 2.70	60.8 ± 30.5	378 ± 205
6 – < 12 y	(16)	2.69 ± 1.21	73.2 ± 16.4	537 ± 166
12 – 18 y	(21)	2.61 ± 1.32	76.6 ± 37.9	685 ± 417[D]
p-value[B]		–	–	0.011
< 2 y[C]	*(6)*	*3.60 ± 4.41*	*46.8 ± 19.8*	*260 ± 85.9*
Month 3				
< 6 y	(15)	2.96 ± 1.76	65.2 ± 21.5	475 ± 178
6 – < 12 y	(15)	2.36 ± 1.07	75.1 ± 20.4	529 ± 169
12 – 18 y	(17)	2.93 ± 1.68	86.5 ± 36.9	790 ± 402[E]
p-value[B]		–	–	0.006
< 2 y[C]	*(4)*	*3.48 ±3.04*	*55.0 ± 24.3*	*412 ± 151*
Month 9				
< 6 y	(12)	2.75 ± 1.85	64.8 ± 17.6	453 ± 132
6 – < 12 y	(11)	2.20 ± 0.918	76.2 ± 22.4	546 ± 181
12 – 18 y	(14)	2.85 ± 1.12	84.2 ± 24.2	680 ± 212
p-value[B]		–	–	0.011
< 2 y[C]	*(4)*	*3.48 ±3.00*	*61.1 ±23.8*	*445 ±94.5*

A C_{max} and AUC_{0-12} are adjusted to a dose of 600 mg/m^2.

B p-value represents the combined p-value for the three major age groups, and is noted only if significant ($p < 0.05$).

C The < 2 year group is a subset of the < 6 year group; no statistical comparisons were made.

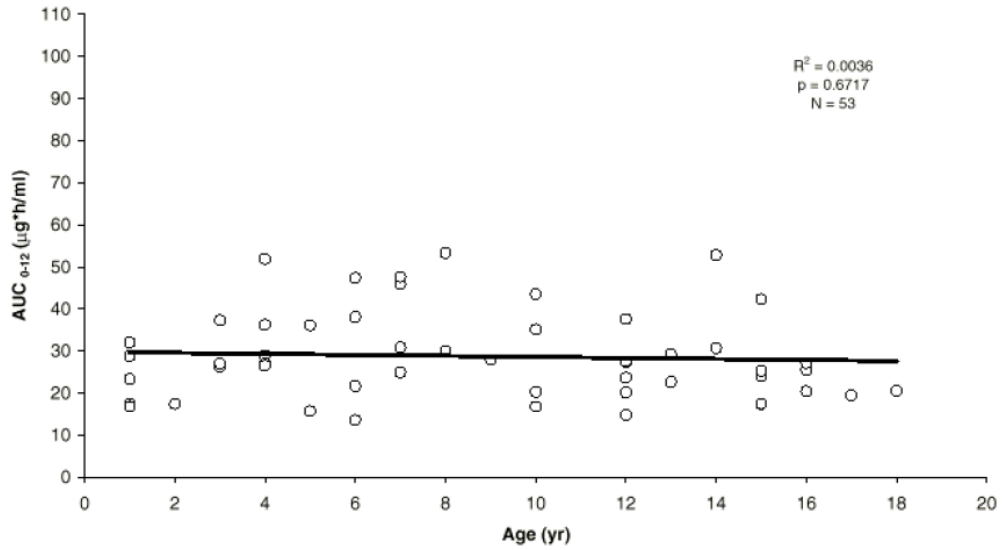
D n = 20

E n = 16

Table 11 Listing of Patients Less Than Two Years Old: Pooled Data from Studies MYCS2190V1 and MYCS2675

		MPA					MPAG										
	Subject Number	Dose Adj. AUC_{0-12} (µg*h/ml)	AUC_{0-12} (µg*h/ml)	Dose Adj. Cmax (µg/ml)	Cmax (µg/ml)	Tmax (h)	Dose Adj. AUC_{0-12} (µg*h/ml)	AUC_{0-12} (µg*h/ml)	Dose Adj. Cmax (µg/ml)	Cmax (µg/ml)	Tmax (h)	Dose (mg/m^2)	AGE (yr)	RACE	SEX	HEIGHT (cm)	WEIGHT (kg)
Day 7	[redacted]	23.3	23.1	11.5	11.4	1.03	323.	321.	55.9	55.5	2.02	596.	1yr 6 mo	CAUCASIAN	FEMALE	78.3	10.3
		28.8	28.0	17.9	17.4	0.500	278.	270.	59.2	57.5	1.50	583.	1yr 3mo	CAUCASIAN	MALE	72.5	11.3
		17.4	16.9	1.79	1.74	12.6	158.	153.	18.6	18.1	12.6	583.	1yr 4 mo	CAUCASIAN	FEMALE	76.5	10.7
		16.8	15.2	11.9	10.7	1.05	178.	161.	32.4	29.3	1.50	542.	1yr 10mo	CAUCASIAN	FEMALE	74.0	11.2
		32.0	32.5	13.6	13.8	1.50	382.	388.	73.2	74.2	2.00	609.	1yr 9mo	CAUCASIAN	MALE	77.3	10.0
		16.8	17.1	5.46	5.57	1.50	239.	244.	41.4	42.2	2.00	612.	1yr 11mo	CAUCASIAN	FEMALE	74.0	11.5
Day 14		9.67	6.94	4.67	3.35	0.500	103.	73.8	21.1	15.1	2.00	431.	1yr 8 mo	HISPANIC	MALE	45.0	9.70
	Mean	20.7	20.0	9.54	9.14	2.67	237.	230.	43.1	41.7	3.37	565.	1yr 7mo			71.1	10.7
	Std.Dev.	7.80	8.59	5.71	5.75	4.39	98.3	108.	20.5	22.1	4.07	63.7	3mo			11.7	0.695
	%CV	37.7	43.0	59.9	63.0	165.	41.4	47.0	47.6	52.9	121.	11.3	15.8			16.4	6.51
	Min	9.67	6.94	1.79	1.74	0.500	103.	73.8	18.6	15.1	1.50	431.	1yr 3mo			45.0	9.70
	Max	32.0	32.5	17.9	17.4	12.6	382.	388.	73.2	74.2	12.6	612.	1yr 11mo			78.3	11.5
	N	7	7	7	7	7	7	7	7	7	7	7	7			7	7
	95% CI	[14.9, 26.5]	[13.6, 26.3]														

Figure 2 Dose Adjusted MPA AUC on Day 7 Versus Age (Study MYCS2675)



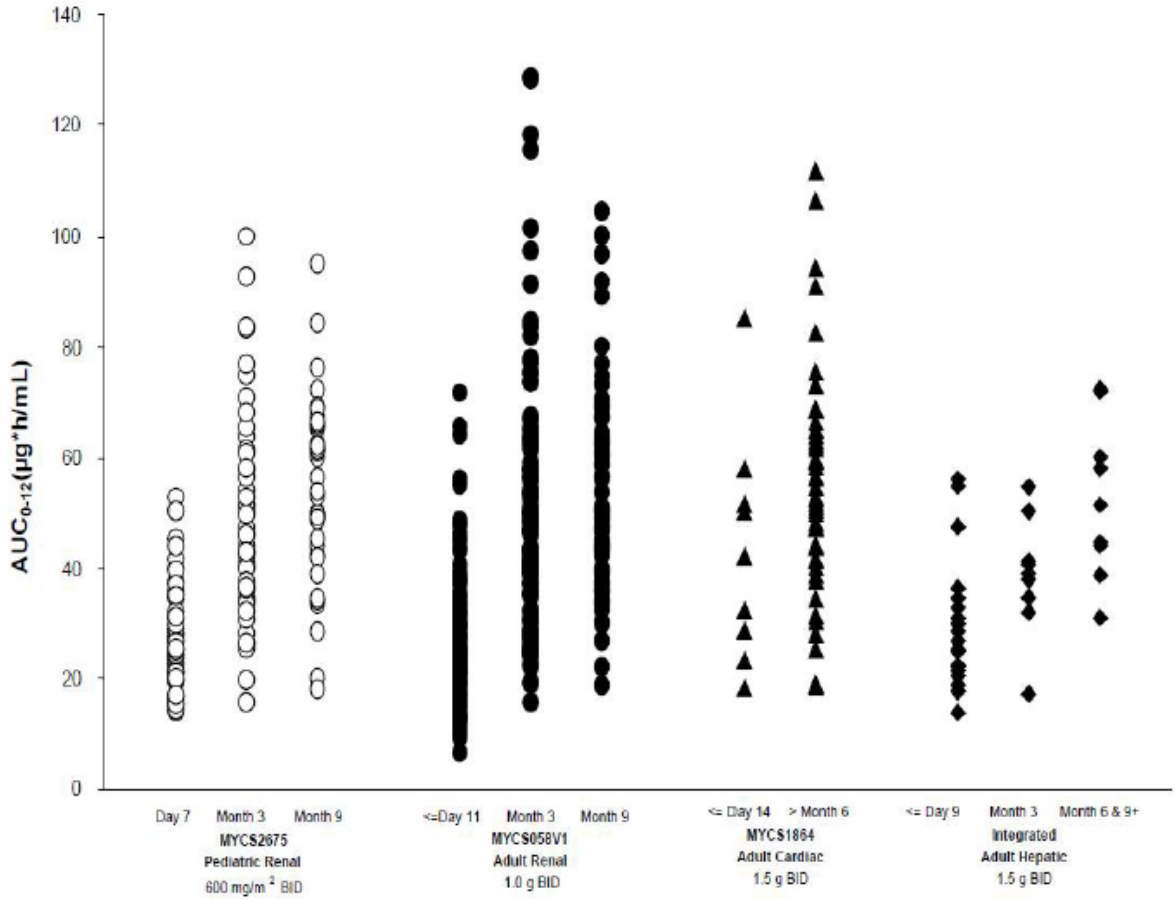
Source: PDBS GAN - AUC_CMAX_AGE.XLS.AUC-D7 (12/14/99 5:21 PM) -- Page 1 of 1

In summary, data generated in Roche-sponsored studies and available in the literature show that there is no difference in the mean PK characteristics of MMF/MPA in paediatric transplant patients across the age group of 1-18 years. At the recommended dosage, the same therapeutic target exposure is reached independent of patient age.

Comparison of MPA exposure in paediatric RTx and adult RTx, LTx and HTx studies

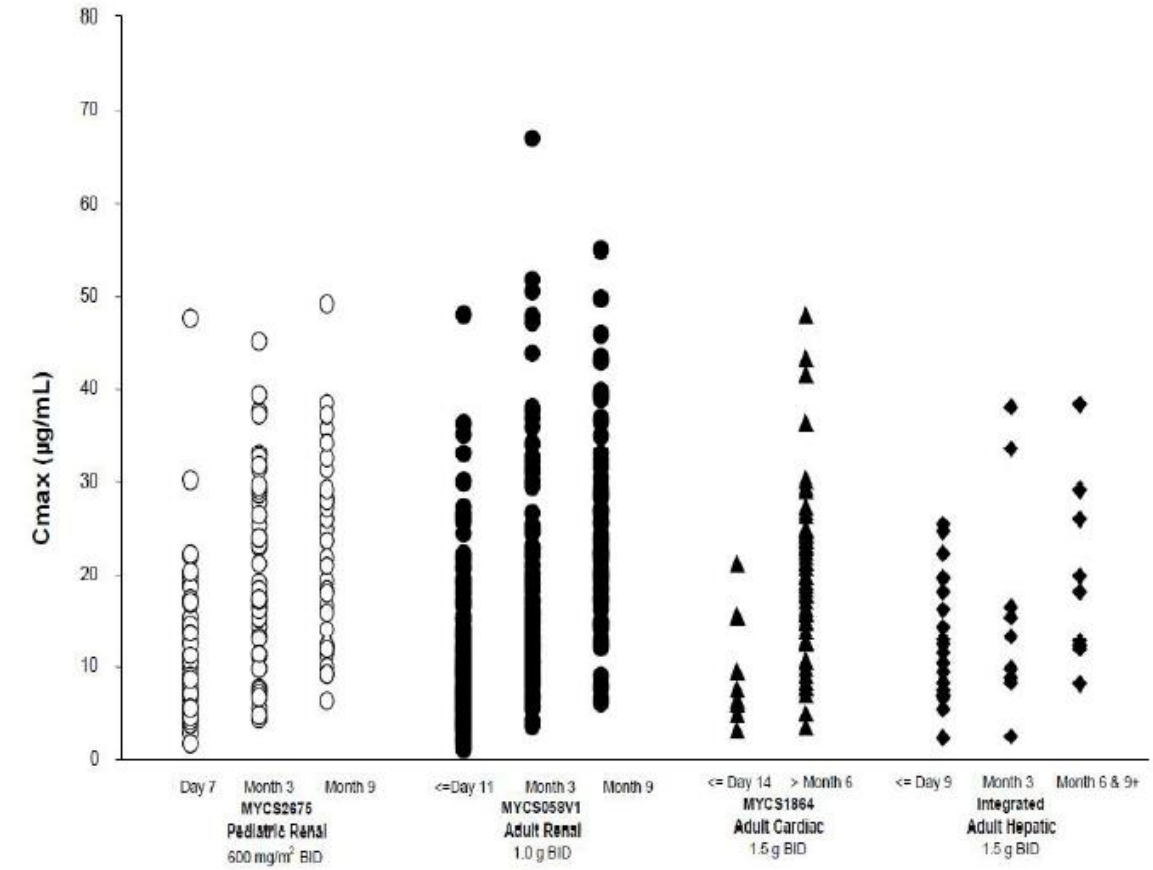
Data collected earlier by the MAH to support the paediatric renal transplantation indication allowed to compare paediatric renal transplant MPA $AUC_{0\text{-}12h}$ (**Figure 3**) and Cmax (**Figure 4**) from Study MYCS2675 to adult transplant data, including cardiac and hepatic transplant data in addition to transport. The adult cardiac and hepatic transplant data in this comparison are derived from patients who received a CellCept dose of 1.5 g b.i.d. In such cardiac transplant patients, the MPA $AUC_{0\text{-}12h}$ is expected to be ~33% higher than in renal patients receiving 1 g b.i.d. and this is indeed observed in the cardiac data. However, in hepatic transplant patients given CellCept 1.5 g b.i.d., the non-dose-adjusted MPA exposure was similar to renal transplant patients adjusted to a CellCept dose of 1 g b.i.d., in the early post-transplant period. As shown in **Figure 3** and **Figure 4** the MPA exposure in paediatric renal transplant patients from Study MYCS2675 is superimposable on data from adult renal transplant patient as well as adult patients with cardiac or hepatic transplants receiving CellCept doses up to 1.5 g b.i.d. over time. From these comparisons it was concluded that the MPA $AUC_{0\text{-}12h}$ resulting from a paediatric dose of 600 mg/m2 overlays almost completely that for 1 g b.i.d. in adult renal patients as well as 1–1.5 g b.i.d. in adults with renal, cardiac, and hepatic transplants in both the early and late post-transplant periods.

Figure 3 Comparison of Mycophenolic Acid AUC_{0-12h} from Paediatric Renal and Adult Renal, Cardiac, and Hepatic Transplant Studies



AUC_{0-12h}=area under the concentration-time curve from time 0 h to 12 h; b.i.d.=twice a day.

Figure 4 Comparison of Mycophenolic Acid Cmax from Paediatric Renal and Adult Renal, Cardiac and Hepatic Transplant Studies



b.i.d.=twice a day; C_{max}=maximum concentration.

Paediatric liver transplantation

Clinical pharmacology experience in paediatric liver transplantation comes mainly from open-label, mostly retrospective studies published in the literature. A single PK study in liver transplant children for dose finding was conducted by Roche (Study PA16497); its results are consistent with the literature reports. The collective PK experience with MPA in liver transplanted children can be compared with findings from similar studies in paediatric kidney transplant patients as previously conducted by Roche (Study MYC2190 and Study MYCS2675) or as reported in the literature.

Clinical study PA16497 in paediatric liver transplants patients

This was an open label, multi-centre, non-controlled study in paediatric liver transplant patients. A total of 9 patients were enrolled in the study (5 females, 4 males), see **Table 12** below. One patient was prematurely withdrawn. Six out of 8 patients were less than 24 months old and the youngest child was 9 months old. Patients had to have received stable MMF dosing (> 6 months of MMF dosing) for at least seven days in order to get a steady-state concentration-time profile. A single 12-hour plasma profile of MPA was then obtained, and MPA $AUC_{0\text{-}12h}$ was calculated.

Table 12 Listing of patient demographic data by trial treatment and CRTN/Patient Number

CRTN/Pt. No.	Age yr	Sex	Weight kg	Height cm	Race	Treatment Start End	Age (months) at Screening	Age of donor (years)	Type of donor
[redacted]	1	M	14	84	CAUCASIAN/ WHITE	21MAR2004 21MAR2004	18	31	LIVING RELATED
	1	F	11	76	CAUCASIAN/ WHITE	16NOV2004 17NOV2004	15	22	LIVING RELATED
	1	F	10	76	CAUCASIAN/ WHITE	07MAY2003 08MAY2003	18	10	CADAVERIC
	2	M	15	85	BLACK	07MAY2003 08MAY2003	24	3	CADAVERIC
	1	M	11	73	CAUCASIAN/ WHITE	16JUL2003 17JUL2003	17	17	LIVING RELATED
	0	M	8	71	MIDDLE EAST EGYPTIAN	14MAY2003 15MAY2003	9	2	CADAVERIC
	5	F	12	86	HISPANIC	25JUN2003 26JUN2003	60	37	LIVING RELATED
	0	F	8	72	CAUCASIAN/ WHITE	10MAR2004 11MAR2004	10	38	CADAVERIC
	1	F	12	75	ORIENTAL	07APR2004 08APR2004	14	25	LIVING RELATED

CRTN = Clinical Research Task Number (center no.)
For processing, missing TT end date and time are replaced by TT start date and time.
DM01 11MAY2005:14:43:52 (1 of 1)

In this study, paediatric liver transplant patients received MMF doses of 200-424 mg/m2. These doses were all lower than the approved dose for paediatric renal transplantation (600 mg/m2). MMF doses in the study were reduced over time from initial post transplantation doses, in line with standard practice at the participating centres, and the PK study was performed at a point when patients were on stable doses. No patient had the MMF dose reduced because of AEs.

The administered doses generated AUCs (dose-normalized) of MPA of less than value of 58 μg·h/mL (late posttransplant target) in 7 out of 8 cases when one patient excluded as outlier, see **Table 13** below. The only patient who achieved an AUC greater than 58 μg·h/mL was considered an outlier because his AUC of 195 μg·h/mL was more than 2-fold higher than that of all the other patients.

Table 13 Individual Raw and Dose-Normalised MPA PK Parameters (Excluding Outlier)

					Normalised to 600mg/m²	
Patient	Dose MMF (mg/m²)	T_{max} (h)	C_{max} (µg/mL)	AUC_{0-12h} (µg·h/mL)	C_{max} (µg/mL)	AUC_{0-12h} (µg·h/mL)
[redacted]	304	2.03	10.0	30.9	19.7	60.9
	424	0.50	12.1	37.2	17.1	52.7
	370	1.95	9.28	25.2	15.1	40.9
	236	0.52	5.96	11.0*	15.2	28.1*
	313	0.63	4.61	14.0	8.85	26.8
	200	2.00	5.61	29.1	16.8	87.2
	213	0.75	3.07	11.5	8.66	32.5
Mean		1.20	7.23	22.7	14.5	47.0
SD		0.75	3.27	10.5	4.21	21.8
CV%		62.6	45.2	46.3	29.1	46.4
Median		0.75	5.96	25.2	15.2	40.9
Min		0.50	3.07	11.0	8.66	26.8
Max		2.03	12.1	37.2	19.7	87.2
Geo Mean		1.00	6.58	20.4	13.9	43.2

AUC_{0-12h}=area under the plasma concentration-time curve from time 0 h to time 12 h; C_{max}=maximum concentration; CV=coefficient of variation; MMF=mycophenolate mofetil; MPA=mycophenolic acid; PK=pharmacokinetic; SD=standard deviation.

Note: * = [redacted] had a BLQ at 12 h which was assigned as Missing. The AUC_{0-12h} (AUC_{τ}) value calculated for this patient was 11.4 µg·h/mL and the AUC_{last} value was 11.0 µg·h/mL. Because there was less than 5% difference between these two values the AUC_{last} value was substituted for AUC_{0-12h} (AUC_{τ}) so that an estimate of AUC for this patient was reported rather than recording it as not calculable due to no measurable MPA plasma concentration result beyond 8 h.

The adjusted AUC for a dose of 600 mg/m² (excluding the youngest patient) was 47.0 µg·h/mL (based on the arithmetic mean) and 43.2 µg·h/mL (based on the geometric mean). To achieve the target AUC of 58 µg·h/mL, a dose in the range of: [(58 µg·h/mL / [47.0 or 43.2 µg·h/mL]) * 600 mg/m²] = 740-806 mg/m² would therefore be required.

In this study, paediatric patients appeared to be relatively under-dosed at 6 months post-transplant compared to the adult population. The dose of CellCept administered to patients was determined by their BSA at transplant and was not adjusted to increasing BSA over time. However, as the majority of patients in this study were between 1 and 2 years of age at the time of transplant, it is expected that their body weight would increase significantly in the 6-month period between transplant and enrolment in this study. Therefore, it is likely that patients were under-dosed as no dose adjustment was made for this increase in body weight.

Literature references of MMF in paediatric liver transplantation

The results of the literature search of paediatric liver transplantation studies are summarised in introduction 2.3.1 of this report.

Publication of Barau et al. 2011

In an attempt to optimise the dosing regimen of MMF in paediatric liver transplant recipients, Barau et al. (2011) determined the MMF dosage required to achieve an $AUC_{0\text{-}12h}$ of >30 h·mg/L. A PK study of 15 children (median age 8.3 years, range 1.1–15.2 years) was performed at a median of 11.0 months (range 0.5–88.0 months) after liver transplantation, see **Table 14** below. The authors concluded from their study that an initial MMF dose of 600 mg/m2 twice a day led to MPA $AUC_{0\text{-}12h}$ values greater than the minimum targeted threshold of 30 h·mg/L. Considering the inter-individual variability of MPA PK, therapeutic drug monitoring was recommended to optimise the daily MMF dosage.

Table 14 MPA $AUC_{0\text{-}12h}$ Values and MMF Doses Before and After Dose Adjustments in Patients Receiving Tacrolimus, cyclosporine, and Rifampin

	Before the Dose Adjustment			After the Dose Adjustment		
	MMF Dose (mg/m^2 Twice a Day)	MMF Dose (mg/kg Twice a Day)	MPA AUC (mg·hour/L)	MMF Dose (mg/m^2 Twice a Day)	MMF Dose (mg/kg Twice a Day)	MPA AUC (mg·hour/L)
Patients receiving tacrolimus						
2	351	10.6	7.3	755	23.8	39.4
3	302	13.7	11.3	596	26.8	45.0
4	300	10.2	12.0	682	24.4	31.8
5	235	10.3	12.9	557	24.2	28.5
6	205	9.7	15.4	511	24.3	37.9
7	265	9.1	19.9	442	15.2	34.0
8	455	15.6	6.8	909	31.3	65.6
9	186	8.3	5.8	371	16.7	39.3
10	421	24.0	35.0	617	24	41.1
11	205	6.1	6.9	1014	30.2	68.7
14	554	20.8	41.6	571	21.7	39.5
Median (range)	300 (186-554)	10.3 (6.1-20.8)	12.0 (5.8-41.6)	596 (371-1014)	24.2 (15.2-31.3)	39.4 (28.5-68.7)
Patients receiving cyclosporine						
1	426	40.0	10.2	851	40	91.8
12	435	14.7	11.7	652	22.1	39.5
Patients receiving rifampin along with immunosuppressive therapy						
13	391	16.7	14.6	782	33.4	13.0
15	295	10.0	9.2	615	20.9	14.8

Publication by Ueno et al. 2020

In a recent study, Ueno et al. (2020) investigated dosing needs, efficacy and safety of MMF in five infants younger than 1 year (mean 8 [range 3–10] months) of age at transplantation, who received living-donor liver transplants. The initial dose was 40-50 mg/kg/day, which was increased to a target MPA trough level of 2 mg/L. The patients also received TAC and, after at least 4 months post transplantation, steroids. The mean final daily MMF dose was 66 (range 47–106) mg/kg or 1430 (range 1280–1920) mg/m^2. According to linear regression analyses, the target Ctrough level of 2 mg/L was reached at a daily MMF dose of approximately 1200 mg/m^2 or 50 mg/kg. In the children younger than 1 year of age a higher dose than in older children was needed to achieve the same exposure target. A dose of 1200 mg/m^2/day was minimally needed to maintain efficacious concentrations.

Literature references of paediatric heart transplantation

There are no Roche-sponsored studies available on the pharmacokinetics and/or pharmacodynamics of CellCept in paediatric HTx patients. However, studies published in the public domain support the conclusions that the pharmacokinetic and metabolic processes underlying MPA absorption and disposition as described for adult HTx patient are equally applicable to paediatric patients.

The literature studies available for evaluation of the PK in HTx children are all based on retrospective analyses and on measurements of trough (pre-dose) levels, and not full pharmacokinetic profiles (Dipchand et al. 2001; Gajarski et al. 2004,). Their focus was on the dose-concentration relationship to determine whether the recommended dose for paediatric RTx children, 600 mg/m2 b.i.d., was sufficient to achieve therapeutic exposures also in HTx children. The concomitant CNI administered in these studies overall was more often CsA than TAC; nevertheless, inclusion of patients on both types of CNI allowed for a comparison of MPA levels achieved and confirmation that indeed MPA levels in presence of TAC were higher than in presence of CsA in paediatric HTx patients.

Publication by Dipchand et al. (2001)

The study by Dipchand et al. (2001) is based on a review of 128 trough levels collected from 44 paediatric HTx recipients (age at transplant 7 days to 18.4 years). It evaluated MPA doses which were required to achieve a target trough concentration of >3 mg/L, a level which had previously been found adequate by Meiser et al. (1997, 1999) to prevent acute rejection episodes in adult heart allograft recipients co-treated with TAC and corticosteroids. Dipchand et al. (2001) showed that daily doses of MMF required in children of 5 years to over 16 years were close to 1800 mg/m2, corresponding to a 3 g/day dose in an adult patient. Younger children required somewhat higher doses, depending on the age range considered, see **Table 15** and **Table 16** below, from the publication of Dipchand et al.

Table 15 Dose of MPA required to achieve therapeutic level* by age

	Age range				
	0 to 1 year	1 to 5 years	5 to 10 years	10 to 16 years	>16 years
# of patients†	11	10	9	8	6
# of patients with therapeutic level	3	4	7	5	5
# of therapeutic levels*	4	4	10	14	7
Dose to achieve therapeutic level					
mg/kg	125 ± 29	101 ± 51	67 ± 31	47 ± 24	49 ± 17
mg/m^2	2,189 ± 696	2,254 ± 887	1,833 ± 931	1,573 ± 833	1,792 ± 579

*Therapeutic level: >3 ng/ml.
†Number of patients in that age range on the date of MPA level.

Table 16 MPA levels in patients on cyclosporine versus tacrolimus by age group

	MMF dose (mg/kg)			MMF dose (mg/m^2)		
	5 to 10 years	10 to 16 years	>16 years	5 to 10 years	10 to 16 years	>16 years
Cyclosporine						
MMF (mean ± SD)	71 ± 24	54 ± 14	44 ± 14	1,956 ± 663	1651 ± 498	1,576 ± 476
MMF median	68	57	41	1,832	1,693	1,497
MMF range	35 to 115	26 to 81	30 to 68	957 to 3132	803 to 2730	1,085 to 2411
Tacrolimus						
MMF (mean ± SD)	41 ± 10	46 ± 11	41 ± 21	1,000 ± 329	1,498 ± 373	1484 ± 700
MMF median	42	49	42	974	1,627	1,620
MMF range	27 to 52	22 to 58	13 to 67	627 to 1429	717 to 1820	534 to 2366

MMF, mycophenolate mofetil.

The age-dependency of MMF dosing could later also be demonstrated by Filler's group (Yoo et al. 2016) analysing 2639 MPA trough levels collected from 37 paediatric RTx recipients co-treated with TAC over 6.6-14 years post-transplantation. Patients at younger age were at greater risk for under-immunosuppression than older children. Therefore, higher starting doses of 1800 mg/m2 (900 mg/m2 b.i.d) of MMF or even more in combination with TAC in children <6 years of age were recommended by Filler's group.

Publication by Gajarski et al. (2004)

In the study by Gajarski et al. (2004) a total of 120 trough levels from 10 children and 10 adults (from one months to 33 years) were available. In this study paediatric doses were at 1200 mg/day (600 mg b.i.d); target MPA concentrations in the study were set at 1.0-3.5 mg/L. As expected, TAC co-administration led to higher MPA levels than CsA (3.0 ± 2.2 mg/L vs. 1.6 ± 1.5 mg/L). Levels of >2.5 mg/L in the study were found to be associated with lower biopsy grades. However, the 1200 mg/m2 dosing failed to achieve levels >1 mg/L in 50% of the patients.

MPA target exposure measures, MPA Ctrough and the standard $AUC_{0\text{-}12hr}$

It is generally agreed that the inter-dosing interval MPA $AUC_{0\text{-}12h}$ is the most reliable index of risk for acute rejection and that the correlation between trough (pre-dose) MPA values and the full AUC (Shaw et al. 2001; Shaw et al. 2003; Filler and Mai 2000) or between trough levels and rejection (Oellerich et al. 2000) are inferior. As it is impractical to collect a full set of timed plasma samples over a 12-h dosing interval, limited sampling strategies have been proposed to estimate the full $AUC_{0\text{-}12h}$ from only a few well-timed collected samples. Also, the clinical utility of MPA trough values have been evaluated; Shaw et al. (2003) applied a target range of 1-3.5 mg/L for adult patients with concomitant CsA, and 1.7-4.0 mg/L with tacrolimus (TAC).

Similar exposure ranges (AUC0-12h 30-60 h • mg/L; trough concentration [Ctrough] 1.5-3 mg/L) as established in adults have been confirmed in paediatric renal (Oellerich et al. 2000; Weber et al. 1998, Weber et al. 2002; Filler et al. 2008), heart (Dipchand et al. 2001; Gajarski et al. 2004; Rauschenfels et al. 2009), and liver (Aw et al. 2003; Ueno et al. 2020) transplant patients. In some of these studies, a correlation of trough concentration with a measure of AUC was found.

The most comprehensive studies on MPA's PK/PD relationship were conducted by Weber et al. (2002) in paediatric renal transplant patients aged 2.2-17.8 years on an immunosuppressive regimen with CsA, MMF, and corticosteroids. This study established the therapeutic ranges for both, MPA-AUC0-12h values

and trough MPA levels in this patient population. MMF was administered orally at a dose of 600 mg/m2 BSA twice a day up to a maximum of 2 g/day. The analyses of the collected information on total and unbound drug showed that both MPA-AUC0-12h and trough MPA levels are statistically significantly associated with the risk of acute rejection in this patient population. According to the study results, for minimizing the risk of rejection after transplantation, total MPA-AUC values in the early stages post-transplant should be maintained within the therapeutic window of 30-60 h • mg/L, or the trough concentration in the range of 1-3.5 mg/L.

Similar to paediatric renal transplant patients, Aw et al. (2003) established a good correlation between an (abbreviated) 7-hour AUC and trough levels in 21 paediatric stable liver transplant patients aged 2-16 years ($r = 0.84$, $p < 0.001$). From the data shown, it appears that a trough concentration range of 1.5-3 mg/L corresponds to an AUC0-7 range of 30-60 h • mg/L.

When Filler (2006) analyzed pre-dose trough levels and full AUCs from 161 patients with variable pathologies (paediatric heart, liver, and kidney transplant recipients as well as patients with autoimmune diseases), there was a weak, but significant correlation between the pre-dose morning trough level and the AUC.

In conclusion, from these studies across transplant indications, it appears that target exposures of AUC_{0-12h} 30-60 h • mg/L and Ctrough 1.5-3 mg/L are associated with prevention of acute rejection not only in adult, but also in paediatric patients.

Dose recommendation and rationale in paediatric heart and liver transplant patients

The collective experience from Roche-sponsored studies and studies from the literature outlined here supports the following dosing recommendation for paediatric heart and liver transplant patients:

The recommended starting dose for cardiac and hepatic paediatric patients is 600 mg/m2 (of body surface area) of MMF powder for oral suspension, administered twice daily (maximum total daily dose of 2 g or 10 ml).

The dose and product form should be individualised based on clinical assessment. Oral solid product forms (capsules and tablets) should not be used by patients unable to swallow them and/or with a body surface area lower than 1.25 m2 due to the increased risk of choking in this age group. Patients with a body surface area of 1.25 to 1.5 m2 may be prescribed MMF capsules at a dose of 750 mg twice daily (1.5 g daily dose). Patients with a body surface area greater than 1.5 m2 may be prescribed MMF capsules or tablets at a dose of 1 g twice daily (2 g daily dose).

For paediatric cardiac and hepatic transplant patients, if the recommended starting dose is well tolerated, the maintenance dose can be increased to 900 mg/m2 body surface area twice daily (maximum total daily dose of 3 g or 15 ml). The dose should be individualised based on clinical assessment.

These dosing recommendations are based on the relationship between exposure to MPA and prevention of rejection as established in adult kidney transplant patients to determine the appropriate dosing of MMF (Study MYC058), see Exposure target in adult reference population.

The target exposure (AUC_{0-12h}) of 27.2 h·mg/L established in Study MYC058 was used to select not only the appropriate dose in Roche's renal transplant program, but also guided dosing in paediatric liver transplant patients.

An exposure-response relationship for desired (prevention of rejection) or undesired (AEs) effects as established in adult renal transplant patients, was not found in Roche-sponsored studies in adult heart or liver transplant patients, most likely due to an insufficient number of study participants and/or high

intersubject variability. Based on the assumption of independence of the mechanism of action of transplanted organ, dosing in these populations was therefore guided to achieve the same exposure range (30-60 h·mg/L) as in renal adult transplant patients. Roche-sponsored clinical studies and clinical studies from the literature have shown that not only the pharmacodynamics, but also the pharmacokinetics of MPA in adults is comparable across transplant indications.

The same guiding principle, namely to determine the doses required to achieve the same target exposure in paediatric as in adult patients and to determine the doses required to achieve that target was applied to treatment of paediatric heart and liver transplant recipients. The underlying assumption, that the same exposure in children as in adults will lead to the same therapeutic effect, was rationalised by the results from studies performed by Roche in support of the registration of CellCept in both adult kidney transplantation and paediatric kidney transplantation. These studies revealed a good scalability of dosing across age groups when comparing adult renal with paediatric renal patients. This scalability is further corroborated by published literature reports. It is rooted in the comparable absorption and disposition behaviour of MPA in adult and paediatric patients and on an age-independent receptor responsiveness.

Off-label use of MMF in 1-2-year-old transplant patients

Transplantation in 1- to 2-year-old patients is always a singular event and pharmacotherapy will have to take into account all patient and treatment factors that determine outcome of the intervention.

The dosing scheme of 600 mg/m2 b.i.d. for paediatric renal transplant patients (corresponding to the 1 g b.i.d. dose in an adult with BSA of 1.73 m2) has been used successfully over the last 20 years in several countries and thus has been validated over a long period of time. However, individually applied dosing schemes vary widely.

Nine reports for 1-2-year-old renal transplant patients were received between 1 January 2000 and 30 September 2023. Sufficient daily dosage information was provided for 7 patients; doses were in the range 600-2041 mg/m2 (average 1119 mg/m2 per day), including multiple dosing regimens for two patients. Hence, these infants received on average the recommended daily dose of 1200 mg/m2; the distribution of individual doses showed that most of the infants received a lower dose than recommended. No events of transplant rejection were reported; one patient on MMF 140 mg b.i.d. (daily dose based on the average BSA for a 1-year-old patient: 571 mg/m2), experienced “slightly elevated creatinine” (unspecified, Preferred Term [PT] Blood creatinine increased).

Ten reports for 1-2-year-old liver transplant patients were received between 1 January 2000 and 30 September 2023. Sufficient daily dosage information was provided for 7 patients; doses were in the range of 208-1224 mg/m2 (average 700 mg/m2 per day). One patient on MMF 250 mg daily (510 mg/m2 daily based on age-adjusted average BSA), experienced liver transplant rejection.

While acknowledging the limitations associated with the small number of reports, these data suggest a high variability in the dosage being used in the off-label population of 1-2 years old paediatric patients with renal and liver transplant, and a tendency to underdose these vulnerable patients with obvious consequences in terms of risk of graft rejection and patient’s survival.

Drug-drug interactions

The published literature on paediatric transplant patients does not give information on concomitantly administered (non-immunosuppressive) drugs. Hence, no information on possible drug-drug interactions can be derived from them. However, potential drug interactions applicable to the administration of MMF to paediatric transplant recipients are expected to be the same as those described for the adult transplant population. In general, PK interactions relevant to the use of MMF involve drugs that (1) interfere with

EHC of MPAG/MPA (such as bile-acid sequestrants or antibiotics) or (2) compete with renal tubular secretion of MPAG (such as acyclovir).

2.3.3. Pharmacodynamics

Mechanism of action

Mycophenolic acid (MPA) is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) and inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA.

Two IMPDH isoforms have been identified, isoform type I, which is present in most known cells (including resting human lymphocytes) and isoform type II, which is strongly and predominantly expressed in activated human B- and T-lymphocytes. The type II isoform is nearly five times more sensitive to inhibition by MPA than is the type I isoform.

Because T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines whereas other cell types can utilise salvage pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells.

In addition to its inhibition of IMPDH and the resulting deprivation of lymphocytes, MPA also influences cellular checkpoints responsible for metabolic programming of lymphocytes. It has been shown, using human CD4+ T-cells, that MPA shifts transcriptional activities in lymphocytes from a proliferative state to catabolic processes relevant to metabolism and survival leading to an anergic state of T-cells, whereby the cells become unresponsive to their specific antigen (Guentert et al. 2021).

MMF does not act on the transplanted organ itself. The immunological mechanisms underlying MPA's mechanism of preventing organ rejecting are independent on organ type and are the same in HTx and LTx as in RTx recipients.

Primary and secondary pharmacology

MPA inhibits the activity of inosine monophosphate dehydrogenase (IMPDH) and with this the proliferation of host B and T lymphocytes. The half maximal effective concentration (EC50) values for IMPDH inhibition by MPA in both children and adults (**Table 17**) are in line with the proposed target MPA exposures (Tang et al. 2017). A 40%-60% inhibition of IMPDH may be sufficient for effective immunosuppression (Langman et al. 1996; Fukuda et al. 2011).

Table 17 Comparative EC_{50} Values for Inosine Monophosphate Dehydrogenase Inhibition by Mycophenolic Acid in Renal Transplant Patients

Reference	Age Group[1] (years)		N	EC_{50} (mg/L)
	Range	Mean ± SD		
Fukuda et al. 2011	2.1 – 20.2	12.5 ± 5.3	28	Mean: 0.97 (95% CI: 0.55–1.41)
Tang et al. 2017	19.2 – 58.4	43.7 ± 11.0	54	Median 3.17 (Range 0.84–7.81)
Tang et al. 2017	60.1 – 76.2	65.8 ± 4.9	26	Median 1.54 (Range 0.92–4.50)
Langman et al. 1995 Langman et al. 1996	Adult	NA	5	Range: 2–5
Budde et al. 2007	NA	42 ± 13	21	Mean: 2.96 (95% CI: 2.96–6.15)

EC_{50}=half maximal effective concentration; NA=not available; SD=standard deviation.

[1] renal transplant patients; for EC_{50} determined in vitro using isolated IMPDH see Nowak and Shaw (1997).

Ontogeny

IMPDH does not undergo ontogenic changes in children above 2 years of age. A German study group analysed IMPDH activity in peripheral blood mononuclear cells (PBMCs) in 80 healthy children between the ages of 2.0 and 17.9 years (Rother et al. 2012). No developmental regulation of IMPDH activity in PBMCs in children older than 2 years was observed. Furthermore, pre-transplant IMPDH activity was comparable in children (median [range], 83.8 [39.6-163.0] µmol s-1 mol-1 adenosine monophosphate; n=31) and adults with end-stage renal disease (92.0 [16.7-213], N=81). IMPDH activity in both children and adults was inversely correlated with MPA plasma concentration indicating that MPA inhibits IMPDH activity in children and adults to a comparable extent. IMPDH activity displayed high interindividual variability (coefficient of variation, 41%) during childhood. Others have reported similarly large interpatient variability in IMPDH activity (Langman et al. 1996; Fukuda et al. 2011).

Table 18 Supportive Data from Ontogeny of Inosine Monophosphate Dehydrogenase Activity (Literature References)

Key Evidence				
Literature Reference	Study Design	Formulation/ Dosing	Demographics (number of patients; gender; age; other details)	Key Findings
Rother et al. 2012	Measurement of IMPDH activity in peripheral blood mononuclear cells (PBMC) from healthy children, healthy adult, children and adolescents after renal Tx following MMF dosing.	n.a.	17 children/ adolescents with renal Tx: n = 8 patients (males/females = 7/1) 2.0-11.9 yrs; time post-Tx 16±4 days; BSA 0.68 (0.58-1.25) m^2. n=9 (males/females=4/5) 12.0-18.9 yrs; time post-Tx 17±4 days; BSA 1.27 (1.17-1.82) m^2.	1. There is no pronounced developmental regulation of IMPDH activity in the paediatric population. 2. IMPDH activity did not differ significantly between different age groups from 2 yrs of age to adults. 3. Comparable inhibition of IMPDH activity by MPA in children and adolescents after renal Tx - in accordance with that observed in adult renal transplant recipients. 4. IMPDH inhibition after MMF dosing is rather a function of free MPA than of total MPA.
	Rationale for Strength of Evidence The prospective comparison of IMPDH activity in renally transplanted children and in healthy control subjects (paediatric, adult) along with the determination of the PK/PD profile of MPA in the transplanted children gives very valuable insight into the ontogeny of the target enzyme for MPA's immunosuppressive activity. The study allowed to determine and compare IC50 values between paediatric ages and between early and late post-transplant periods. Noteworthy, an improved assay for IMPDH activity in peripheral blood mononuclear cells (PBMC) was used in this study, which (in contrast to earlier studies) was not potentially falsified by mononuclear cell count. This study provides a mechanistic basis for the empirical observation of comparable effectiveness of MPA at the same exposure across paediatric and adult age groups.			
Supportive Evidence				
Tönshoff et al. 2011	Review article	n.a.	n.a.	1. Ontogeny of IMPDH: There is no change in IMPDH activity with developmental regulation in children older than 2 yrs.
	Rationale for Strength of Evidence The review article by Tönshoff et al. (2011) brings together many of the aspects relevant for immunosuppressive therapy in a paediatric transplant population. The scope of the article is to review the specific paediatric aspects of concentration-controlled MPA dosing in solid organ transplantation (including ontogeny). It stresses the need for therapeutic drug monitoring particularly in patients at high immunological risk (e.g., initial post-transplant period, withdrawal/low dose CNI treatment strategies, steroid avoidance, drug adherence). However, no new data are presented in this article.			

BSA=body surface area; IMPDH=inosine monophosphate dehydrogenase; MMF=mycophenolate mofetil; MPA=mycophenolic acid; PBMC=peripheral blood mononuclear cells; n.a.=not available; Tx=transplant(ation); yrs=years.

Two supporting literature references were provided but none included patients below the age of 2.

2.3.4. Discussion on clinical pharmacology

In this application, the MAH initially applied for an extension of the current paediatric indication of MMF in RTx approved from 2 years of age to include children as of 3 months of age undergoing RTx, HTx and LTx. However, only limited data were available for infants (3 months to 1 year) and there was not enough data to support the justification for the PK comparability of MMF/MPA in infants and the proposed dosing regimen in this population. Therefore, the MAH proposed to revise the indication for an use in paediatric patients from 1 year of age. This was considered acceptable by the CHMP.

For use in children undergoing HTx and LTx, an initial dose of 600 mg/m2 of BSA is proposed and if immunosuppression is insufficient, the dose can be increased to 900 mg/m2. The paediatric extrapolation is primarily based on PK-comparison with the adult reference population and is supported by one paediatric clinical study in liver transplant patients (PA16497), previously submitted paediatric clinical studies in renal transplant patients (MYC2190 and MYCS2675) and by several paediatric studies in the literature in RTx, LTx and HTx.

Based on literature references, the MAH argued that the key ADME processes/parameters of MMF/MMP in paediatric patient above 1 year are comparable to adult patients. Comparability is reasonably justified for children above 1 year, in particular with regards to similarity in metabolic activity of the key enzyme UGT1A9, involved in the clearance of MPA and comparability with regards to plasma protein binding of MPA. Furthermore, key PK characteristics of MPA in adult patients as CsA DDI and non-stationarity were also observed in children. Hence, the PK comparability of MMF/MPA between paediatric and adult population is agreed by the CHMP.

In adult RTx, a reference exposure target value, $AUC_{0\text{-}12h}$, for the active drug MPA in early post-transplant period was established by PK/PD analysis and applied for the renal paediatric PK extrapolation approach and PK-driven extrapolation to adult LTx and HTx. This target exposure value has been shown to provide an optimal benefit in the prevention of organ rejection in combination with an acceptable safety profile. The pharmacokinetics of MMF/MPA in adult RTx was reasonably comparable with HTx and LTx patients, supporting the previous approval for use in these types of transplantation. The recommended dosing in adults is though different: 1.5 g b.i.d. (3 g daily dose) MMF in HTx and LTx compared to 1 g b.i.d. (2 g daily dose) MMF in RTx. A comparable translation from paediatric RTx to paediatric LTx and HTx should therefore also be valid.

In kidney paediatric transplant studies, supporting previous approval for use in 2-18 years old renal transplant patients in combination with ciclosporin and corticosteroid, a paediatric dose of 600 mg/m2 (maximum daily dose of 2 g) was established using the adult reference exposure target value. Body surface area (BSA) based scaling paediatric dosing was demonstrated to be superior to weight-based dosing and it was shown that a BSA based dosing results in reasonably comparable target exposure in RTx paediatric patients from 1 to 18 years. In addition, MPA AUC values across paediatric age groups were similar in the early and late post-transplant period. This information and a summary of the mean PK parameters by age and post-transplant have been included in section 5.2 of the SmPC. In conclusion, the data on MMF/MPA exposure in 1-2 year renal transplantation patients support an extension of the paediatric population to also include children down to 1 year, with the same dose of 600 mg/m2 (maximum daily dose of 2 g) as for RTx paediatric patients above 2 year.

In the clinical study PA16497, conducted in 8 paediatric LTx patients (6 patients < 2 years), it was demonstrated that a slightly higher dose of 740 mg/m2 dose was necessary to reach the late post-transplant target exposure reference value of 58 μg·h/mL A summary of these results has been added in section 5.2 of the SmPC. Overall, the paediatric studies reported in the literature were supportive of the PA16497 study and use of MMF in paediatric LTx patients in combination with ciclosporin and corticosteroid at the initial dose of 600 mg/m2 b.i.d.

Sponsored clinically studies are not available of MMF in paediatric heart transplant patients. The use of MMF in paediatric HTx patients is supported by two literature references (Dipchand et al. (2001) and Gajarski et al. (2004)), which both applied MPA Ctrough target values in their analysis. MMF dosing and MPA Ctrough values in the two publication appear to be in the range with other RTx and LTx paediatric studies. The mean Ctrough level was lower in the group of infants whose exact age is not available, compared to older children. According to the MAH, an early MPA Ctrough value of 1.5-3 mg/L appears as the optimal range. Overall, the paediatric studies reported in the literature were supportive for the use of MMF in paediatric HTx patients in combination with ciclosporin and corticosteroid at the initial dose of 600 mg/m2 b.i.d.

In conclusion, the starting dose of 600 mg/m2 MMF was shown to be adequate in children above 1 years. Data from the study conducted by the MAH and literature reports provides some support for using a higher MMF dose than 600 mg/m2 MMF children with insufficient immunosuppression due to inadequate MPA exposure. The MAH argued for not increasing the initial dose in younger children as the dose of MMF should be adjusted in LTx and HTx patients according to the need of the individual patient. If immunosuppression is assessed as insufficient, a dose increase to 900 mg/m2 twice a day (maximum daily dose of 3 g) is recommended. This recommendation to increase the dose to individual needs is consistent with the recommended adult dose for HTx and LTx, 1.5 g b.i.d. (3 g daily dose). This dosing regimen in LTx and HTx has been adequately justified and is accepted by the CHMP.

Overall, sufficient evidence have been provided to support the use of MMF in paediatric LTx and HTx patients, 1-18 year, and expanding the use in RTx in children down to 1 year. The recommended

paediatric dosing regimen has been reasonably justified by the MAH and is consistent with the adult MMF dosing regimen and the already approved paediatric dosing scheme.

The mechanism of action of MPA is a potent, selective, uncompetitive and reversible inhibition of inosine monophosphate dehydrogenase (IMPDH) and the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. This is independent of transplant type and can be transferred from HTx and LTx and RTx to one another.

The pharmacodynamics relevant for both PD relationship with efficacy as well as safety is as described the IMPDH inhibition typically measured in EC50 levels. Ontogeny has been addressed and thus the claim that the PD is independent of age is accepted by the CHMP.

2.3.5. Conclusions on clinical pharmacology

PK comparability of MMF/MPA in children from 1 to 18 years has been demonstrated for RTx, LTX and HTx. In conclusion, the pharmacokinetic data are sufficient to support the following posology (section 4.2 of the SmPC) of MMF in children from 1 year to 18 year for all 3 types of transplantation:

- The recommended mycophenolate mofetil initial dose for paediatric renal, cardiac and hepatic transplant patients is 600 mg/m2 (of body surface area (BSA)), administered orally, twice daily (initial total daily dose not to exceed 2 g, or 10 ml of the oral suspension).
- The dose and product form should be individualised based on clinical assessment. If the recommended initial dose is well tolerated but does not achieve clinically adequate immunosuppression in paediatric cardiac and hepatic transplant patients, the dose can be increased to 900 mg/m2 BSA twice daily (maximum total daily dose of 3 g, or 15 ml of the oral suspension). The recommended maintenance dose for paediatric renal transplant patients remains at 600 mg/m2 twice daily (maximum total daily dose of 2 g or 10 ml of the oral suspension).

2.4. Clinical efficacy

No new study has been presented for this type II variation. A review of relevant clinical data literature is presented below supporting the application for extension of indication.

According to the MAH, the clinical efficacy data supporting the application originate from available publications of studies conducted in the paediatric population, including 14 studies relevant to paediatric heart transplant (HTx) and 15 studies relevant to paediatric liver transplant (LTx) patients.

In addition, clinical efficacy data from the Roche-sponsored pivotal trials conducted in the adult population, and data extracted from the Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR) Registries for HTx and LTx in the United States (US) are also included to provide the context for interpretation of the available literature data.

The MAH also resubmitted the clinical studies conducted in paediatric renal transplant.

2.4.1. Dose response studies

No new dose-response studies were conducted for this variation application. For background on dosing recommendations please see the PK-section above.

2.4.2. Main studies

Renal Transplantation in Adult Recipients

The pivotal clinical trials with MMF, which formed the basis for approval for use in prevention of organ rejection in adult RTx patients, were three randomised, double-blind, multi-centre trials assessing the safety and efficacy of MMF in combination with corticosteroids and ciclosporin A (CsA): Studies ICM1866, MYC0221, and MYC023.

The pivotal studies compared two dose levels of oral MMF (1 g twice a day [b.i.d.] and 1.5 g b.i.d.) with either azathioprine (AZA; 2 studies) or placebo (1 study) when administered in combination with CsA and corticosteroids to prevent acute rejection episodes.

The primary efficacy endpoint was the proportion of patients in each treatment group that experienced treatment failure within the first 6 months after transplantation.

Treatment failure was defined as:

• Biopsy-proven acute rejection upon treatment, or the occurrence of death or graft loss; or

• Early termination from the study for any reason without prior biopsy-proven rejection. MMF was studied in the following three therapeutic regimens:

a) Anti-thymocyte globulin induction/MMF or AZA/CsA/corticosteroids;

b) MMF or AZA/CsA/corticosteroids;

c) MMF or placebo/CsA/corticosteroids.

The following tables (**Table 19**, **Table 20**, and

Table 21) summarise the results of these studies.

MMF in combination with corticosteroids and CsA significantly reduced the incidence of treatment failure within the first 6 months following transplantation ($p < 0.05$).

More patients receiving MMF discontinued therapy (without prior biopsy-proven rejection, death, or graft loss) than in control groups, with the highest rate in the MMF 3 g/day group. Patients who prematurely discontinued treatment were not followed for the occurrence of acute rejection after termination. Therefore, the acute rejection rates may be underestimated, particularly in the MMF 3 g/day group.

Table 19 Renal Transplant Study ICM1866 (Syntex Report CL 6813): Incidence of Treatment Failure at 6 Months Post-Transplant

US/Canada Study* ICM1866 (N=499)	Mycophenolate mofetil 2 g/day (n = 167)	Mycophenolate mofetil 3 g/day (n = 166)	Azathioprine 1-2 mg/kg/day (n = 166)
All treatment failures	31.1%	31.3%	47.6%
Early termination without prior acute rejection**	9.6%	12.7%	6.0%
BPAR episode on treatment	19.8%	17.5%	38.0%

BPAR = biopsy proven acute rejection on treatment; N = number; US = United States.
*Anti-thymocyte globulin induction/mycophenolate mofetil or azathioprine/ciclosporin A/corticosteroids.
**Does not include death and graft loss as reason for early termination.

Table 20 Renal Transplant Study MYC023 (Syntex Report CL6821): Incidence of Treatment Failure at 6 Months Post-Transplant

Europe/Canada/Australia Study*MYC023 (N=503)	Mycophenolate mofetil 2 g/day (n=173)	Mycophenolate mofetil 3 g/day (n=164)	Azathioprine 100 150 mg/day (n=166)
All treatment failures	38.2%	34.8%	50.0%
Early termination without prior acute rejection**	13.9%	15.2%	10.2%
BPAR episode on treatment	19.7%	15.9%	35.5%

BPAR=biopsy proven acute rejection on treatment; N=number.
*Mycophenolate mofetil or azathioprine/ciclosporin A/corticosteroids.
**Does not include death and graft loss as reason for early termination.

Table 21 Renal Transplant Study MYC022 (Syntex Report CL6819): Incidence of Treatment Failure at 6 Months Post-Transplant

Europe Study*MYC022 (N=491)	Mycophenolate mofetil 2 g/day (n=165)	Mycophenolate mofetil 3 g/day (n=160)	Placebo (n=166)
All treatment failures	30.3%	38.8%	56.0%
Early termination without prior acute rejection**	11.5%	22.5%	7.2%
BPAR episode on treatment	17.0%	13.8%	46.4%

BPAR=biopsy proven acute rejection on treatment; N=number.
*Mycophenolate mofetil or placebo/ciclosporin A/corticosteroids.
**Does not include death and graft loss as reason for early termination.

Cumulative incidence of 12-month graft loss and patient death are presented in **Table 22**. Numerically, patients receiving MMF 2 g/day and 3 g/day experienced a better outcome than controls in all three studies. Patients receiving MMF 2 g/day experienced a better outcome than MMF 3 g/day in two of the three studies. Patients in all treatment groups who terminated treatment early were found to have a higher incidence of graft loss and death at 12 months post transplantation.

Table 22 Cumulative Incidence of Combined Graft Loss and Patient Death at 12 Months Post-Transplant

Study	Mycophenolate mofetil 2 g/day	Mycophenolate mofetil 3 g/day	Control (AZA or placebo)
US ICM1866	8.5%	11.5%	12.2%
Europe/Canada/Australia MYC023	11.7%	11.0%	13.6%
Europe MYC022	8.5%	10.0%	11.5%

AZA=azathioprine; US=United States.

Long-term (1-3 year) efficacy results for Studies MYC023 and MYC022 are summarised in **Table 23**.

Table 23 Long-Term Efficacy Results of Studies MYC023 and MYC022

Study	Treatment group	Graft rejection	Treatment failure	Graft loss	Death
MYC023	Mycophenolate mofetil 2 g/d	34.5%	24%*	15.1%	4.7%
	Mycophenolate mofetil 3 g/d	29.3%	30%*	8.7%	9.2%
	Azathioprine 100-150 mg/d	50.0%	N/A	15.7%	8.8%
MYC022	Mycophenolate mofetil 2 g/d	17.0%**	30.3%**	8.5%	7.3%
	Mycophenolate mofetil 3 g/d	13.8%	38.8%	12.5%	8.1%
	Placebo	46.4%	56.0%	15.7%	10.8%

*Data are reported as a reduction in the proportion of patients with treatment failure compared to azathioprine.

**Data not specified in 3-year report; 12-months results are shown.

Renal Transplantation in Paediatric Recipients

Approval in paediatric patients was based on one open-label, PK, safety and efficacy study in 100 paediatric RTx recipients aged 3 months to 18 years (Study MYCS2675). MMF powder for oral suspension was dosed at 600 mg/m2 b.i.d. (up to 1 g b.i.d.) in all age groups and was combined with CsA and maintenance corticosteroids. The patients were followed for up to 3 years post-transplant. The efficacy data are summarised in **Table 24**.

Table 24 Efficacy Results of Paediatric Renal Transplant Study MYCS2675

	6 month post-transplant	12 months post-transplant	3 years post-transplant
Biopsy-proven rejection*	24%	25%	30%
Graft and patient survival	93%	93%	93%

*Includes biopsy-proven and presumed rejection at 12-month post-transplant.

The study concluded that a 600 mg/m2 MMF dosing regimen provides a predictable PK profile in paediatric RTx patients. The results indicated that MMF treatment in paediatric patients is associated with patient and graft survival rates comparable to those in adult populations.

Evidence of Efficacy in Cardiac Transplantation in Adult Recipients

Approval in adult cardiac transplant patients was based on one randomised, double-blind, multi-centre trial MYCS1864 (Niranjan et al. 2008).

Study MYCS1864 compared the efficacy of MMF and AZA in 578 cardiac transplant recipients. Patients received MMF 1.5 g b.i.d (n=289) or AZA 1.5–3 mg/kg/day (n=289), in combination with CsA and corticosteroids, as maintenance immunosuppressive therapy. No difference was established between MMF (32%) and AZA (35%) with respect to biopsy-proven rejection with hemodynamic compromise (p=0.338). At 3 years, the incidence of death or re-transplantation was 18.3% in AZA-treated patients and 11.8% in MMF-treated patients (difference 6.5%, 95% confidence interval [CI]: 1.1 to 12.0%). The authors

suggested that MMF might provide some benefit in survival compared to AZA in patients who are able to take oral medication in the immediate post-transplant period. Efficacy results are summarised in **Table 25**.

Table 25 Summary of Efficacy Results from Roche Study MYCS1864

Treatment group	Follow-up period	Graft rejection	Death or re-transplantation
Mycophenolate mofetil 3 g/d	3 years	14.5%	11.8%
Azathioprine 1.5-3 mg/kg/d		24.2%	18.3%

Evidence of Efficacy in Hepatic Transplantation in Adult Recipients

Approval in adult hepatic transplant patients was based on one randomised, double-blind, multi-centre trial MYCS2646.

Study MYCS2646 was a randomised, double-blind, parallel-group, multi-centre, comparative study in 564 primary hepatic transplant recipients that was performed at 16 centres in the US, 2 in Canada, 4 in Europe, and 1 in Australia. Patients either received MMF 1 g b.i.d intravenously for up to 14 days followed by MMF 1.5 g b.i.d. orally, or AZA 1–2 mg/kg/day intravenously followed by AZA 1–2 mg/kg/day orally, in combination with CsA and corticosteroids, as maintenance immunosuppressive therapy. Efficacy results are summarised in **Table 26**.

Table 26 Efficacy Results of Study MYCS2646

	Azathioprine (n=287)			Mycophenolate mofetil (n=278)		
	6 months	12 months	3 years	6 months	12 months	3 years
Biopsy-proven and treated rejection or graft loss (death/re-transplantation)	47.7%	50.2%	54.7%	38.1%	42.4%	48.9%
Death or re-transplantation	14.6%	14.6%	19.9%	14.0%	14.7%	21.6%

n=number.

Real World Data from Registries

The off-label use of MMF-containing regimens in paediatric heart and liver transplant recipients has increased over time. In paediatric HTx approximately 93% of children received MMF and for paediatric LTx, 49% of children received MMF as part of an immunosuppressive regiment in 2019. From the literature, use of immunosuppressants (including MMF) in paediatric liver and heart transplant patients is consistent between countries.

Methods

A systematic literature search was conducted in the electronic databases BIOSIS Previews, Derwent Drug File, Embase, Medline, Cochrane Library and NICE website. The literature search was cumulative until end of 2022. The search terms were keywords from MeSH and Emtree thesaurus for clinical studies, clinical trials, meta-analysis, efficacy, effectiveness, treatment outcome, disease progression, evidence-based medicine, guidelines and related concepts, combined with the drug terms 'mycophenolate mofetil', 'cellcept' or 'mmf' in paediatric population with liver and heart transplant(s). A free text search in title and abstract with those terms was also performed. Exclusion criteria were case reports, letters, editorials, notes, preclinical studies and non-English publications. From the 105 publications identified, randomised clinical trials, observational studies, meta-analyses, and guidelines concerning the approved indications

were considered. Reference lists from the identified publications were also examined to identify any relevant information that may have been missed in the systematic search.

Paediatric Heart transplant

A summary of the available publications of studies showing a potential benefit related to the efficacy of MMF when used in paediatric HTx recipients is included in

Table 27, below. The publications are grouped by the potential benefit and provide supportive evidence. This includes 12 retrospective studies and 2 prospective observational studies.

Table 27 Summary of Paediatric Heart Transplant Studies Contributing to Efficacy Evaluation (Supportive Evidence)

Study/ Reference Ranking	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
Rejection					
Dipchand et al. 2001	Single center, retrospective chart review of patients switched from AZA to MMF for rejection, facilitation of steroid dose reduction or cessation or tolerability issues with existing regimen.	The average MMF dose was 40±14 mg/kg. MMF was started in patients taking steroid and AZA; 20/21 patients also received TAC (median dose 0.18 mg/kg, range 0.03–0.64 mg/kg) and 1/21 received CsA (10 mg/kg). AZA was discontinued when MMF initiated. Formulation not specified. Follow-up: median 1.3 years after HTx (range 72 days to 5.4 years).	N=21 Median age at review: 12.3 years (range: 11 months to 16.9 years). Median age at HTx: 10.7 years (range: 55 days to 16.7 years.). MMF started at a median of 4.3 months after HTx (range: 1 day to 4.5 years). Males:females=12 :9	MMF appears to be effective for treatment of rejection in the paediatric heart Tx population and has an acceptable side-effect profile. In addition, it may have a role in primary rejection prophylaxis and may facilitate reduced steroid dosage or steroid-free immunosuppression.	Rejection treatment and prophylaxis. Steroid sparing. Switching form AZA to MMF appears to be effective for the treatment and prevention of organ rejection in HTx. MMF facilitates reduced steroid and steroid free immunosuppression.
	Rationale for Classification of Evidence: This study is a small, single-centre, retrospective chart review.				
Groetzner et. al. 2005	Single center, retrospective study of clinical outcomes.	Pre-1994: CsA, corticosteroids and AZA. Post-1994: TAC or CsA, corticosteroids and AZA. Post-1995: TAC or CsA, corticosteroids and MMF. Target trough levels for 1st year: TAC 11–15 ng/mL, CsA	N=47 (30 with dilated cardiomyopathy, 17 with congenital heart disease). Mean age: 9.4±6.9 years (range: 4 days to 17.9 years).	Freedom from acute rejection after 5 years was 40% with CsA-based immunosuppression, and 56% with TAC-based immunosuppression. Since the introduction of MMF, freedom from acute rejection increased to 62%. Actuarial 1, 5, and 10-year survival was 86%, 80%, and 80%, respectively. Actuarial survival improved significantly since 1995: 1 year: 92% *vs.* 78%; p=0.09; 5 years: 92% vs. 68%; p=0.04	Rejection prophylaxis Since the introduction of MMF freedom from rejection improved significantly.

Study/ Reference Ranking	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
		250–350 ng/mL, mycophenolic acid 2–4 mg/L Formulation: 250 mg/day IV post-operatively, then orally after extubation (oral formulation not specified) Follow-up: mean 5.25±3.6 years	Males:females=29 :18		
	Rationale for Classification of Evidence: This study is a small, single-centre, retrospective review.				
Lammers et al. 2010	Retrospective study of acute rejection to identify predisposing factors, including population risk factors (gender, ethnicity, number of HLA mismatches and ABO mismatch) and immunosuppression regime, as well as factors such as CMV status (and mismatch).	Triple therapy: TAC (or sirolimus, if severe renal dysfunction). Steroid (withdrawn if possible after 2nd negative endomyocardial biopsy). AZA (pre-April 2005) or MMF (post-April 2005). Dose: not specified. Formulation: not specified. Follow-up: mean 2.6±1.6 years (range: 0–5.5)	N=105 (66 dilated cardiomyopathy, 12 restrictive cardiomyopathy, 27 congenital heart disease). Age at Tx: 8.3±5.8 years. Males:females=50 :55	7 patients died (6.7%), 5 during admission Tx from acute graft failure/pulmonary hypertension (4.8%). These 5 patients were censored from further analysis. 50/100 children who survived and were discharged from hospital after their Tx, received TAC and MMF. 6 children received sirolimus and MMF (5 with additional steroid). 31 received TAC and AZA, 13 received TAC without a cell cycle inhibitor (six were on additional steroid). There were 23 episodes (21.9%) of significant rejection in 271.9 patient-years in 21 patients (20%). Sirolimus therapy without a CNI, CMV (IgG) positive status before Tx and non-Caucasian ethnicity was associated with hemodynamically compromising rejection on univariate analysis. None of the patients presenting with hemodynamic collapse was on MMF. Sirolimus was also associated with a higher incidence of symptomatic rejection (p<0.0001) whereas TAC was associated with a lower risk (p<0.0001). The authors found the lowest incidence of rejection with immunosuppressive regimes including TAC and MMF. However, the difference between TAC and MMF vs. TAC and AZA was not statistically different. Authors concluded that TAC+MMF the was regimen of choice and MMF might be protective against rejection resulting in hemodynamic collapse, as none of the patients	Rejection prophylaxis Lower incidence of rejection with TAC and MMF than with TAC and AZA or TAC alone. MMF might be protective against rejection resulting in hemodynamic collapse.

Table 27 continuation

Study/ Reference Ranking	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
				requiring ECMO as rescue therapy for rejection episodes received MMF and no cases of severe hemodynamic compromise were seen TAC+MMF-treated patients.	
	Rationale for Classification of Evidence: This study is a single-centre, retrospective review.				
Marshall et al. 2013	Retrospective, historical-control, observational study to compare outcomes for CsA-AZA-steroid and TAC-MMF.	Pre-April 2008 (control group): CsA-AZA-prednisone without induction Post-April 2008 (new protocol group): TAC-MMF and no steroid maintenance (antithymocyte globulin induction with high-dose steroid for 5 days) Dose: not specified. Formulation: not specified. Follow-up: control group 6.3±1 years, new protocol 3.6±0.6 years.	N=103 (64 control, 39 new protocol). Age at Tx: Control 9.7±6.1 years. New protocol 7.8±6.7 years. Gender not stated.	In the control group, 37/64 subjects (58%) had ≥1 episode of rejection in the first year after Tx, compared with 14/39 subjects (36%) in the new protocol group (OR=0.41, 95% CI: 0.18 to 0.92, p=0.42). Among subjects who were followed for ≥2 years, 2/37 subjects (5%) receiving the new protocol experienced a rejection episode during the second year. In the control group, 2/56 subjects (4%) experienced a rejection episode during the second year (p=0.67). In the control group, 37/64 subjects (58%) had >1 episode of rejection in the first year after Tx, compared with 14/39 subjects (36%) in the new protocol group (OR=0.41, 95% CI: 0.18 to 0.92, p=0.042). Death within the first year after Tx occurred in 8/64 patients (13%) in the control group, compared with only 1/39 patients (3%) in the new protocol group, but the difference was not statistically significant (OR=0.18, 95% CI: 0.022 to 1.53, p=0.15) Overall graft survival was not different between the two groups (p=0.68) but the TAC-MMF regimen was associated with improved freedom from rejection.	Rejection prophylaxis Switching from an AZA containing without induction treatment regimen to a MMF containing one with induction treatment shows significantly less episodes of acute rejection. This benefit extended to 1 year after the HTx.
	Rationale for Classification of Evidence: This is a retrospective observational, single centre study using a historical control which compared outcomes of two different combination treatments.				

Study/ Reference Ranking	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
Lamour et al. 2019	Prospective, multi-institutional observational cohort study of children without DSAs at time of Tx.	Steroid avoidance regimen that included no routine use of corticosteroids beyond the first week after Tx. All patients received thymoglobulin induction therapy (total cumulative dose 7.5 mg/kg) and maintenance immunosuppression with TAC and MMF Dose: data not collected. Formulation: not specified/ Follow-up: minimum of 1 year	N=186 Median age 6 years (range: 1–14) Males:females=90:96	182 subjects survived to hospital discharge, 181 were discharged on TAC. MMF was the sole adjunct immunosuppression in 155 subjects (85.2%) through the first year, and 27 were using AZA in the first year. Probability of patient survival at 1 year was 94.5% (95% CI: 1 to 97). In the first year post Tx, 58 subjects (31.2%) had an acute rejection event, and 21 subjects (11.3%) had recurrent rejection (>2 episodes). Freedom from acute cellular rejection was 78.6%, AMR 94.4% and rejection with hemodynamic compromise 97.1%. Multivariable logistic regression model identified risk factors for acute cellular rejection that included older age (p=0.0055) and non-black race (p=0.059), whereas a separate multivariable logistic model identified risk factors for any rejection that included older age (p=0.0117), non-black race (p=0.0043), and presence of non-DSA antibodies before Tx (p=0.0527). New onset diabetes was observed in 3 subjects (1.6%).	Rejection prophylaxis Steroid sparing HTx recipients without DSAs at transplant, and managed with a steroid avoidance regimen, have excellent short-term survival and low risk of first-year diabetes mellitus and PTLD when treated with MMF as part of their maintenance immunosuppressive regimen.
	Rationale for Classification of Evidence: This is a prospective, multi-centre observational study, provides supportive evidence and was not designed to assess the efficacy or effectiveness of MMF.				
Cardiac Allograft Vasculopathy					
Moffett et al. 2014	Single center retrospective analysis of patients whose HTx was performed between 1996 and 2012, with the aim to identify the effect of the different immunosuppressive regimens on the development of CAV.	Patients who received different medication regimens were followed to 1 of 3 endpoints: date of first CAV diagnosis, reTx or death. CAV was determined by angiography/imaging or pathology. Medication regimens included: CsA, TAC, MMF, sirolimus, prednisone, statin, beta-blockers and ACE inhibitors. Medication regimen in those that developed CAV was compared to patients that had not developed CAV.	N=148. Age <19 years Males:females=57%: 43%	Graft loss occurred in 27% patients and CAV was present in 24% patients. Median time to Patients were excluded if death occurred prior to first clinic visit, not transplanted at institution, had multi-organ Tx, or reTx. Statistical analysis included univariate and multivariate hazard models. Median time to CAV was 5.52 years (range: 1.0–12.3). No difference was seen in patients who developed CAV to those who had not with respect to age at HTx, sex, or CMV status. Of those who developed CAV, 97% were on steroids compared to 78% without CAV; 26% patients who developed CAV were on MMF compared to 60% without CAV. Multivariate HR showed that statins and MMF were protective from the development of CAV (HR=0.39 and HR=0.45, respectively).	CAV prophylaxis The use of MMF has a protective effect against the development of CAV in paediatric recipients of HTx.
	Rationale for Classification of Evidence: Retrospective analysis evaluating the effect of different regimens on the development of CAV.				

Table 27 continuation

Study/ Reference Ranking	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
Renal Sparing					
Boyer et al. 2005	Prospective study in paediatric patients receiving CNI and AZA who developed a progressive decline in renal function >2 years after cardiac Tx.	CNI dose reduced by 50% and AZA replaced by MMF. MMF 300 mg/m^2 b.i.d, increased after 1 week to 600 mg/m^2 b.i.d. Formulation: not specified. Follow-up: mean 26.3 months (range: 15–36).	14/52 paediatric cardiac Tx recipients received MMF due to renal decline (age at Tx: 0.5–204 months). Males:females=6:8	Inulin clearance in the 14 children receiving MMF decreased from 84.2 mL/min/1.73m^2 at 1 year post-Tx to 46.5±9.6 mL/min/1.73 m^2 at the time of change in immunosuppressive therapy. Significant renal lesions were observed in renal biopsies performed prior to the change. At 1 year, inulin clearance had increased by 67%. In 6 patients who had a second determination 2 years after the switch, inulin clearance was not significantly different from the value at 1 year. There were three reversible acute rejection episodes in three patients. The incidence of rejection episodes was not different from a control group of patients whose treatment was not changed. The reduction of CNI dosage and replacement of AZA by MMF is a safe way to improve renal function in children with heart Tx and CNI-induced nephrotoxicity.	Renal sparing CNI reduction and replacement of AZA with MMF improved renal function.
	Rationale for Classification of Evidence: This is a prospective, single-centre, observational study evaluating the renal sparing potential of CNI free regimens.				
Rosenthal et al. 2021	A single-center retrospective analysis to assess the safety of long-term CNI-free immunosuppression with regard to survival, graft failure, and the impact on renal function in paediatric HTx patients.	Patients that discontinued CNI were maintained on MMF and everolimus without the use of corticosteroids. The median follow-up time after switch of immunosuppression regiment was 6 years (range: 0–11). CNI was discontinued after a median time of 9years (range: 3–14).	N=15	Rejection surveillance was performed with annual catheterization for evaluation of hemodynamics and endomyocardial biopsy. Serum creatinine levels and estimated glomerular filtration rates were analyzed to assess renal function. Median survival time after transplantation was 15 years (range: 5–23). One patient died of acute humoral rejection 15 years after Tx, the other 14 patients were alive with good graft function. No increased rejection rate could be observed after discontinuation of CNI. Serum creatinine levels significantly decreased and estimated glomerular filtration significantly increased. CNI discontinued maintenance therapy appears to be safe in paediatric HTx recipients with no increased risk of rejection or death and leads to significant recovery of impaired renal function.	Renal sparing Discontinuation of CNIs under a MMF and TAC immunosuppressive regimen is safe and leads to significant improvement of renal function.
	Rationale for Classification of Evidence: This study is a single-centre retrospective study evaluating the renal sparing potential of CNI free regimens.				

Study/ Reference Ranking	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
Steroid Sparing					
Singh et al. 2010	Retrospective study evaluating early outcomes of steroid avoidance immunosuppression.	All patients received induction with thymoglobulin 1.5 mg/kg/dose and treatment with IV steroid. Dose: Patients were treated with oral TAC based on age and MMF 1,200 mg/m^2 per day divided in 2 or 3 doses. MMF dose was adjusted to achieve a target trough level of 2-4 mg/dL Formulation: not specified Follow up: median 19 months (range: 2–46)	N=55 Median age: 7.1 years (range: 2 weeks to 22 years). Males:females=27:28	50 patients survived to discharge after Tx. Of these, 2 patients (4%) were discharged on steroids, and 8 patients (16%) started maintenance steroids at follow-up. Rejection was diagnosed in 8 patients (cellular rejection in 3 patients and AMR in 5). Freedom from rejection was 92% at 6 months (95% CI: 80 to 97) and 87% at 1 yr (95% CI 73–94). Post Tx survival was 91% at 6 months and 88% at 12 and 24 months (95% CI: 75 to 95). There was 1 death due to AMR 8 months after Tx.	Steroid sparing A steroid avoidance immunosuppression protocol containing MMF was associated with low incidence of rejection during the first year after transplant in paediatric HTx recipients.
	Rationale for Classification of Evidence: This is a two-centre retrospective study evaluating the potential of MMF containing regimens to enable steroid sparing.				

Table 27 continuation

Study/ Reference Ranking	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
ABO Incompatible Transplant					
Urschel et. al. 2013	Multi-center, retrospective survey (Canada, UK, Germany and US) of ABOi HTx.	Induction immunosuppression included anti-thymocyte globulin (61%), basiliximab (32%) or none (7%). All patients received CNIs (90% TAC, 10% CsA), 62% with MMF, 10% with AZA, 2% with everolimus and 24% with steroids. Dose: not specified. Formulation: not specified. Follow-up: median 37.7 months (range: 0.46–117)	N=58 Age at Tx: 6.8 months (range: 0.03–90). Males/Females=30:28	Graft survival was 100%/96%/69% at 1/5/10 years, respectively. Two patients died in the follow-up period. One due to acute multi-organ failure with systemic infection while listed for re-Tx for severe graft vasculopathy at 5.5 years post-Tx. The other patient died due to combined cellular rejection and AMR associated with donor-specific HLA antibodies and positive lymphocyte crossmatch but minimal serum antibodies to the donor BG (highest anti-B titers pre- and post-Tx: 1:2), 85 days post-Tx. Two patients underwent reTx. One graft (A into O recipient), reTx after 5.7 years, had developed refractory hypertrophic obstructive cardiomyopathy and mitral regurgitation with unsuccessful surgical repair. The other reTx was performed after 6.5 years (an AB donor into an A recipient) due to chronic graft failure. Children who lost their grafts did not show a specific pattern with regard to demographic data, pre-Tx history and induction or maintenance immunosuppression. All were <1 year old at the time of Tx and none had reported titers of circulating antibodies to donor BG of >1:4 post-Tx. None of these 4 graft losses was attributed to ABOi by the clinical team. Authors concluded that successful ABOi HTx can be performed at an older age and with higher isohemagglutinin titers than initially assumed and using similar immunosuppressive regimens as for ABO-compatible Tx. Rejection and graft vasculopathy are rare.	ABOi transplant ABOi HTx with immunosuppressive regimens containing MMF is feasible in children under 8 years old.
	Rationale for Classification of Evidence: This study is a multi-centre retrospective survey evaluating the possibility of MMF containing regimens to enable ABOi HTx.				

Study/ Reference Ranking	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
Other MMF Benefits					
Nunoda et al. 2013 (Abstract)	Single center retrospective review.	Patients received standard triple therapy including CsA or TAC, MMF, and a corticosteroid. Five of 26 patients received proliferation signal inhibitors (one with sirolimus and four with everolimus) during the late post-transplant period. Dose: not specified. Formulation: not specified. Follow up: 9.24±5.54 years.	N=26 Age at Tx: 7.6±4.2 years. Males:females=16:10	Patient survival at 1, 5, 10, and 20 years post-Tx was 96.2%, 91.3%, 85.3%, and 85.3%, respectively. During the follow-up period, one patient died of CAV at 4.8 years, and one due to PTLD at 7.3 years, one suffered primary graft failure and received reTx two days later. Pediatric survival rates were better than those observed in the centers for the adult cohort: survival rates were 94.7%, 94.7%, 81.2%, and 72.2% at 1, 5, 10, and 15 years post-Tx). Growth in patients returned to normal after Tx. 25 of 26 patients (96%) required no activity limitation after Tx and returned to school, one patient required total assistance due to a post-Tx stroke.	Long-term follow-up
	Rationale for Classification of Evidence: This is a single-centre retrospective review providing long term follow up data on patients who received MMF containing regimens.				
Li et al. 2015	Single center retrospective chart review.	Maintenance immunotherapy comprised CsA, MMF and steroid before 2011 and TAC, MMF and steroid from 2011. Dose: not specified. Formulation: not specified. Follow-up 1-70 months.	N=19 Age at Tx: mean 12.6 years, median 15 years (range: 3 months to 18 years). Males:females=10:9	The overall survival after Tx for the pediatric population is approximately 90% at 1 year. The survival rate during hospitalization was 100% at this center. All patients were followed after discharge. The follow-up time ranged from 1 month to 70 months. Only one patient suddenly died of primary graft failure. There was no graft vascular disease or lymphoproliferative disease during follow-up.	Benefits in Chinese population MMF used as part the immunosuppression regimen of Chinese HTx patients.
	Rationale for Classification of Evidence: This is a single-centre retrospective chart review of patients who received MMF containing regimens.				

Table 27 continuation

Study/ Reference Ranking	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
Castleberry et al. 2017	Survey based assessment of clinical practice patterns between pediatric Tx centers.	Dose: data not collected. Formulation: data not collected. Follow-up: data not collected.	Data not collected.	The response rate was 77% (40 responses from 52 contacted centers, 37 with complete responses). The majority of respondents were from Tx centers located in the US (36/40, 90%) other participants were from the UK (2/40, 5%), Canada (1/40, 2.5%), and Brazil (1/40, 2.5%). Most centers reported TAC (36/38, 95%) and MMF (36/38, 95%) as maintenance immunosuppression. The median number of heart Tx performed annually was 8 (IQR of 3–19), and median volume over the past 3 years was 25 (IQR of 7–57). Clinicians at 58% of centers (23/40) were willing to accept a positive cross-match donor for sensitized patients, and 87% centers (33/38) would perform ABOi Txs in infants. The survey found that there was a high level of uniformity and agreement on maintenance immunosuppression and treatment of rejection.	Other benefits A majority of clinical protocols at pediatric centers across the US and other international centers reported utilizing TAC and MMF (36/38, 95% for both) for most patients as part of their long-term maintenance immunosuppression treatment.
	Rationale for Classification of Evidence: This is a retrospective survey assessment across centres of the regimens used.				

Table 27 continuation

Study/ Reference Ranking	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
Haregu et al. 2021 (abstract)	One center, retrospective review of 12 highly sensitized HTx candidates who underwent desensitization therapy at the University of Virginia Hospital between 2014 and 2020.	The majority of patients received an oral immunosuppressive regimen of prednisone (0.3 mg/kg/day to max dose of 12.5 mg) and an antimetabolite (CellCept 60 mg/kg/dose Q12 up to 1,000 mg Q12 or Imuran 1-2 mg/kg/day) followed by a single infusion of rituximab (37 mg/m^2) and monthly IVIG (2 g/kg) infusions; plasmapheresis was used in one patient and bortezomib was used in two.	N=12	Calculated panel reactive antibodies decreased by an average of nearly 20% after an average of 17.5 weeks. HLA I antibodies were more susceptible to desensitization than HLA II antibodies (60% vs 36% average antibody reduction, respectively). Immunosuppression medications were well tolerated with only one patient requiring rituximab discontinuation due to hypotension, tachycardia and respiratory distress. There were no cases of AMR in those patients who underwent Tx. In this cohort, B-cell/ antibody targeted therapies were safe and effective in improving allosensitization and allowing for successful Tx, though HLA II antibodies were more resistant to therapy.	Desensitization therapy Desensitization therapy in paediatric HTx candidates is feasible using B-cell/ antibody targeted therapies and an immunosuppressive regimen containing steroids and MMF.
	Rationale for Classification of Evidence: This is a single-centre retrospective review of MMF containing regimens used in desensitisation.				

AMR = antibody mediated rejection; AZA = azathioprine; b.i.d. = twice a day; CI = confidence interval; CNI = calcineurin inhibitor; CMV = cytomegalovirus; CsA = ciclosporin A; DSA = donor-specific antibodies; ECMO = extracorporeal membrane oxygenation; HLA = human leucocyte antigen; HR = hazard ratio; HTx = heart transplant(ation); IgG = immunoglobuline G; IQR = interquartile range; IV = intravenous; IVIG = intravenous immunoglobulin; MMF = mycophenolate mofetil; OR = odds ratio; PTLD = post-transplant lymphoproliferative disorder; reTx = retransplantation; TAC = tacrolimus; Tx = transplant(ation); US = United States.

Paediatric Liver Transplantation

A summary of the available publications of studies showing a potential benefit related to the efficacy of MMF when used in paediatric LTx recipients is included in **Table 28**, below. The publications are grouped by the potential benefit and provide supportive evidence. This includes 8 retrospective studies and 7 prospective (mainly observational or single arm) studies.

Table 28 Summary of Paediatric Liver Transplant Studies Contributing to Efficacy Evaluation (Supportive Evidence)

Study/ Reference	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
Rejection					
Chardot et al. 2001	Retrospective analysis.	Median initial oral dose of MMF: 23 mg/kg/day (range: 12–43). Formulation: not specified Follow-up: median follow-up after initiation of MMF 642 days (range: 229–1606).	N=19 Median age at Tx: 30 months (range: 7–149) Males:females=8:11.	MMF was indicated for rejection or insufficient immunosuppression in 16 cases, with normalization of both liver function tests and liver histology in 10 cases (62%). MMF was successfully used in one patient with post-Tx immune hepatitis and one patient with steroid dependence. In three patients with renal function impairment, MMF allowed reduction of CsA or TAC dose without subsequent rejection.	Rescue for allograft rejection MMF is effective for paediatric LTx recipients with rejection or insufficient immunosuppression.
	Rationale for Classification of Evidence: This is a single-centre retrospective analysis on the use of MMF as rescue in children with insufficient immunosuppression or allograft rejection.				
Aw et al. 2008	Retrospective single arm study on long-term outcome of the use of MMF to rescue liver allografts with steroid resistant biopsy-proven cellular rejection.	MMF was added at a dose of 10 mg/kg/day in divided doses, and the dose was increased to a maximum of 40 mg/kg/day over 2 weeks. Follow-up: median 8.8 years (range: 7.7–11.5).	N=26 children (28 Txs) Age at Tx: 1.7 years (range: 0.4–13.6) Males:females=10:16	Primary immunosuppression was CsA-based triple therapy in 22 children and TAC-based dual therapy in 6 children. 25 children had been converted to TAC prior to the addition of MMF. The median time to MMF rescue was 1.8 months (range: 0.4–35.8), with patients having received a median of 2 courses of high-dose steroid. 21 out of the 28 episodes of steroid resistant rejection showed an initial positive response to MMF. The median follow-up was 8.8 years (range: 7.7–11.5). In responders, there was 1 death from PTLD, no grafts were lost to chronic rejection. In the 7 non-responders, 3 grafts were lost due to chronic rejection, and 2 resulted in death. Surviving children were clinically well, with good liver function, and 17 remained on MMF. Three children had glomerular filtration <80 mL/min/1.73m^2.	Rescue for allograft rejection MMF is effective in treating steroid resistant acute allograft rejection in paediatric LTx recipients.
	Rationale for Classification of Evidence: This is a retrospective single-arm study evaluating the use of MMF in rescue of steroid resistant rejection.				

Study/ Reference	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
Renal Sparing					
Aw et al. 2001	Prospective study of the efficacy of MMF enabling CNI reduction in pediatric LTx recipients with CNI-related nephrotoxicity without an increased rejection rate.	MMF 20 mg/kg/day in two divided doses for 1 week Increased to 40 mg/kg/day in two divided doses after 1 week. CsA/TAC doses reduced Formulation: not specified Study period: 12 months Median follow up: 24 months after introduction of MMF	N=14 Median age at Tx: 4.2 years (range: 0.9–13.8) Gender not specified	The median (range) GFR in ml/min/1.73 m^2 increased from a baseline of 52 (31–71), to 69 (38–111) at 6 months and 73 (35–98) at 12 months (p=0.00014). At the time of study entry, 13 children were still on CsA and one had been converted to TAC. Ten of these children were still on CsA at the end of the study period. Side effects of MMF include leucopenia in two and backache in one, two of whom discontinued MMF. Acute allograft rejection occurred in three children. All 14 were well with a median follow-up of 24 months (range: 14-38) from MMF introduction. Paediatric LTx recipients with stable graft function and CNI-related nephrotoxicity may benefit from the addition of MMF to their immunosuppressive regimen, with consequent reduction of the CNI dose. Ideally this treatment modification should be attempted before GFR deteriorates to <50 ml/min/1.73 m^2	Renal sparing The addition of MMF to the immunosuppressive regimen of children with CNI-related nephrotoxicity allows reduction of CNI dose and recovery of renal function with a 21% incidence of allograft rejection.
	Rationale for Classification of Evidence: This is a single-arm prospective study evaluating the potential for MMF to enable CNI reduction and recovery of renal function.				
Nobili et al. 2003	The consequences of introducing MMF and reduction of CNI in LTx children was analysed. CNI reduced and MMF added in patients transplanted ≥5 years ago with stable graft function and renal dysfunction. Serum creatinine, uric acid concentration, azotemia and creatinine clearance before and 6 months after study entry were measured.	Dose: initial dose of MMF 20 mg/kg/day in two divided doses increased to 40 mg/kg/day during first month Formulation: not specified Follow-up: 6 months	N=8 Mean age: 13 years. (range: 10–15) Males:females=4:4	Six months after study entry, serum creatinine, uric acid concentration, azotemia and creatinine clearance improved in all the patients. Aspartate aminotransferase and alanine aminotransferase concentrations were stable during the study period and serum bilirubin did not increase. The results indicate that renal dysfunction significantly improved when MMF therapy is started and CNI reduced.	Renal sparing The addition of MMF to the immunosuppressive regimen of children with CNI related nephrotoxicity allows reduction of CNI dose and recovery of renal function
	Rationale for Classification of Evidence: This is a single-arm prospective study evaluating the potential for MMF to enable CNI reduction and recovery of renal function.				

Table 28 continuation

Study/ Reference	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
Ferraris et al. 2004	Prospective evaluation of the incidence of chronic renal dysfunction in patients >5 years old. After LTx and benefit of decreased CsA dose + introduction of MMF on renal function and immune response.	MMF dose: 600 mg/m^2 b.i.d Formulation: not specified. Follow-up: 1 year after CsA dose reduction and introduction of MMF.	Tx recipients: N=60 Survival >5 years: N=50 Patients with chronic renal dysfunction: N=14 Patients included in study: N=11 (Males:females=5:6) Mean age at study: 12.5±2 years.	14 patients developed chronic renal dysfunction secondary to CsA toxicity as evaluated by renal biopsy. In 11/14, CsA dose was decreased to 40–90 mg/mL target levels, and MMF added to regimen. Plasma creatinine decreased (from 1.0±0.03 to 0.8±0.03 ng/dL, p<0.007), creatinine clearance increased (from 66.8±3.0 to 99.2±6.3 mL/min/1.73 m^2, p<0.002), and microalbuminuria decreased (from 21.0±8.6 to 3.6±1.1 mg/24 h, p<0.05) after 12 months of CsA combined with MMF therapy. During combined therapy, the proliferative, cytolytic response and cytotoxic antibodies showed no significant changes, whereas CD4/CD8 ratio increased (from 1.2±0.2 to 1.4±0.1, p<0.05). Tumor necrosis factor-alpha secretion increased (p<0.005) during MMF therapy. The release of interleukin-10 was strikingly augmented under both immunosuppressive regimens, but the release of transforming growth factor-beta and interferon-gamma did not change. Authors concluded that initiation of MMF combined with reduced doses of CsA allowed the recovery of renal function with minor changes in the immune response.	Renal sparing For children with CsA induced renal dysfunction the addition of MMF allowed the dose of CsA to be reduced with an improvement in renal function and no apparent increase in the risk of rejection.
	Rationale for Classification of Evidence: This is a single-centre prospective study evaluating the potential for MMF to enable CNI reduction and recovery of renal function.				
Evans et al. 2005	Retrospective analysis of the effect of MMF on renal dysfunction after LTx.	MMF monotherapy (n=36) MMF with steroids (n=4) MMF with low dose CsA or TAC (n=8) Dose: up to 40 mg/kg per day in 2 divided doses. Formulation: not specified. Follow-up: 1 year.	N=48 Age: median 11.1 years (range: 0.9–18.1) Males:females=23:25	In 92% children with renal dysfunction after paediatric LTx, MMF treatment provided safe and effective immunosuppression and allowed CsA or TAC to be discontinued or reduced, leading to improvement of renal function. The improvement was greatest in younger children and those who began MMF early post-LTx. Side effects were uncommon. Author concluded that additional steroid cover during the transfer to MMF should be considered to prevent liver-allograft rejection.	Renal sparing The addition of MMF to the immunosuppressive regimen of children with CNI related nephrotoxicity allows reduction of CNI dose and recovery of renal function.
	Rationale for Classification of Evidence: This is a single-centre retrospective analysis evaluating the potential for MMF to enable CNI reduction and recovery of renal function.				

Study/ Reference	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
Tannuri et al. 2007	Retrospective analysis on the use of MMF in children with LTx and impaired renal function due to CNI.	Dose: The usual immunosuppression was CsA) with glucocorticoid In 2001, protocol was changed to TAC with glucocorticoid. MMF was added at 10 mg/kg b.i.d, and increased to 40 mg/kg/day over 2 weeks. CNI dosage was reduced to 50% of baseline dosage over 1 month. Formulation: not specified. Follow-up: 24 months.	N=11 Age range: 3 –15 years. Males:females=5:6	The time interval between LTx and the introduction of MMF varied from one year and four months to 12 years and six months. Nine patients (82%) showed improvement of all renal function parameters after introduction of MMF and reduction of CNI dosages, in comparison with the pre-treatment values. The two patients that did not show any improvement in renal function parameters had the longest interval of time between Tx and the introduction of MMF (11 and 12 years). All parameters of liver function remained unchanged. No episodes of acute or chronic rejection during the period were detected.	Renal sparing The addition of MMF to the immunosuppressive regimen of children with CNI related nephrotoxicity allows reduction of CNI dose and recovery of renal function.
	Rationale for Classification of Evidence: This is a single-centre retrospective analysis evaluating the potential for MMF to enable CNI reduction and recovery of renal function.				

Table 28 continuation

Study/ Reference	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
Leiskau et al. 2018	Single center matched cohort study (2 age and diagnosis matched patients for each study patient, one of them treated with TAC and one with CsA and steroids).	Dose: MMF started 7 days post-Tx at a dose of 10 mg/kg in 2 doses for 2 weeks gradually increased to max dose of 20 mg/kg (max 2x750mg) in 2 doses. Formulation: not specified. Follow-up: 1 year after Tx.	MMF+TAC: N=19 Age at Tx: 6 years and 9 months (range: 3 months to 16 years 6 months). Males:females=10:9 TAC: N=19 Age at Tx: 5 years and 7 months (range: 7 months to 16 years and 11 months). Males:females=7:12 CsA+steroids: N=19 Age: 5 years, 5 months (range: 5 months to 15 years and 9 months). Males:females=9:10	All patients survived for the 1st year. All patients survived for the first year after LTx. Graft survival was 89.5% MMF+TAC; 94.8% CSA and TAC groups, respectively (p=0.55). In both the MMF+TAC and the TAC group, BPAR (RAI score ≥3) in 31.5% of cases during the first year after LTx. In the CSA group, 42.1% of the patients suffered from BPAR (OR=1.50; 95% CI: 0.42 to 5.44; p=0.52). No cases of chronic rejection were observed. All groups showed a significant deterioration in renal function post-Tx with the nadir at 3 months, and stabilization achieved by 12-months. No significant differences in creatinine GFR or estimated GFR between the 3 groups were seen at any time during the observation period. Results differ from observations of Tannuri and Evans, who saw an improvement of renal function shortly following the commencement of MMF treatment post-Tx. Notably, most of these patients received MMF monotherapy. Other studies documenting better renal function observed an improvement only after several years. The reduction of TAC might not be sufficient to notice a renal benefit. The authors note that in previous paediatric studies MMF was introduced in patients with CNI-induced renal dysfunction, whereas in this study, patients received de novo MMF therapy.	Renal sparing Benefit of using TAC and MMF de novo in paediatric LTx recipients was not supported.
	Rationale for Classification of Evidence: This is a single-centre comparison of MMF containing regimen with an historic CNI comparator arm.				
Steroid Sparing					
Teisseyre et al. 2011 (Abstract)	Prospective study to compare TAC plus MMF (Group A) to TAC plus steroids (Group B) in children after LTx.	Group A: MMF from Day 0 to Day 90, then reduced and discontinued 4 months after Tx. Group B: steroids according to a low-dose scheme, after 7 months steroid withdrawal initiated. Dose: not specified. Formulation: not specified. Follow-up: 3 years.	Group A: 22 patients aged 0.2–18 years. Group B: 22 patients aged 0.12–18.1 years. Gender not stated.	Liver and renal function, blood glucose and incidence of CMV infections were similar in both groups at 1, 2 and 3 years after Tx. Group A vs Group B: showed a reduced need for antihypertensive treatment (p<0.05) early and at 1 and 2 years post-Tx. Lower incidence of EBV infection in 1, 2 and 3 years after Tx (p<0.05). Acute rejection episodes more frequent in second years post-Tx (p<0.05). More patients showed normal liver histology one year post-Tx however this difference was not significant. Steroid resistant acute rejection was not seen in either group. Immunosuppression using a regimen with TAC and MMF but without steroids is feasible and safe in children after LTx.	Steroid sparing Immunosuppression without steroids is feasible post LTx.
	Rationale for Classification of Evidence: This is a single-centre prospective study evaluating the use of MMF in enabling steroid sparing.				

Study/ Reference	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
ABO Incompatible Transplant					
Schukfeh et al. 2015	Single center, prospective study comparing patients receiving ABOi LTx to patients receiving ABO-compatible Tx in the same period.	Dose: Immunosuppressive regimen for all patients consisted of IV or oral steroid (initially 15 mg/m^2 days 1–10 postoperatively), TAC (from 2 x 0.05 to 0.1 mg/kg) orally, and MMF (2 x 10 mg/m^2 orally since Day 3) Formulation: oral – precise formulation not specified. Follow-up: median 2.6 years (range: 1–4.5).	ABOi N=6 Age: median 13 months (range: 6–30). Males:females=4:2 ABO compatible N=6 matched patients	ABOi group: patient and graft survival 83%. One female patient died within 24 hours due to fulminant gram-negative sepsis. Another patient developed acute cellular rejection at the 8th postoperative day, which responded to steroid treatment. No further complications occurred. ABO-compatible group: patient survival 100%, graft survival 83%. One patient received re-transplantation after 4 days.	ABOi transplant ABOi living related LTx using TAC and MMF based immunosuppression is feasible in children under 3 years of age.
	Rationale for Classification of Evidence: This is a single-centre prospective study evaluating the use of MMF containing regimens in facilitating ABOi transplant.				

Table 28 continuation

Study/ Reference	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
Mysore et al. 2018	Single center retrospective comparison of Tx outcomes in ABO-compatible and ABOi LTx patients.	For ABOi patients immunosuppressive regimen determined by IH titers. Dose: Patients with high IH titer (≥1:32): enhanced immunosuppressive regimen including plasmapheresis, rituximab, IVIG, and MMF (15 mg/kg b.i.d). Patients with low IH titers (≤1:16): steroids and TAC. Formulation: not specified. Follow-up: 3 years.	ABO-compatible control group N=19 Median age: 13.5 months (range: 8.2–20.6) ABOi group N=10 Median age: 8.9 months (range: 5.1 months to 9.3 years). Males:females=5:5	Rates of complications (rejection, infections, biliary, and vascular) at both 1 year and up to 3 years post-Tx were comparable between the groups. Patients with ABOi LTx had good graft function, with 100% survival at a median follow-up of 3.3 years. The study was not designed to compare efficacy of immunosuppressive regimens, but demonstrated that in high risk ABOi patients, a regimen based on IH titers (with intensive immunosuppressive regimens including MMF being administered in case of high IH titers) resulted in complication rates comparable to those seen in lower risk ABO compatible controls.	ABOi transplant ABOi transplant using immunosuppressive protocols tailored to IH titres is feasible.
	Rationale for Classification of Evidence: This is a single-centre retrospective study evaluating the use of MMF containing regimens in facilitating ABOi transplant.				

Study/ Reference	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
Dhungel et al. 2019	Single center retrospective study of children receiving ABOi LTx.	Dose: MMF not specified, started 1 week before Tx. MMF, TAC and CS used post operatively. Formulation: not specified. Protocol consisted of rituximab 2 weeks prior (>3 years) and plasmapheresis before LTx.	N=8 Median age: 31 months (range: 7–91) Gender: not specified.	Patient and graft survival was 100% in recipients at a mean follow-up of 33 months (range: 2–80).	ABOi transplant ABOi transplant using immunosuppressive protocols containing MMF are feasible.
	Rationale for Classification of Evidence: This is a single-centre retrospective study evaluating the use of MMF containing regimens in facilitating ABOi transplant.				
Other MMF Benefits					
Shen et al. 2008	Single center retrospective analysis of indications, surgical techniques and post-operative management.	Dose: MMF not specified. Formulation: not specified. Follow-up: mean 21.8 months	N=31 Age at Tx: 12.4 years (range: 5 months to 18 years).	30/31 patients received TAC + MMF + steroids. 1/31 patients received CsA-based regimen. 5/31 patients died during perioperative period (mortality rate 16.1%). Postoperative complications in 10 patients included biliary leakage, acute rejection, abdominal infection, hepatitis B virus or hepatitis C virus infection, and pulmonary infection. Cumulative survival rate at 1-, 3-, and 5-years was 78.1%, 62.6%, and 62.6%, respectively.	Use in a Chinese paediatric population
	Rationale for Classification of Evidence: This is a single-centre retrospective study reporting outcomes in a Chinese population who received MMF containing regimens.				

Table 28 continuation

Study/ Reference	Study Design	Dosing, Formulation, Duration	Demographics	Key Findings	Key Benefit
Xinias et al. 2010	Single center retrospective case review	Dose: CsA (2-6 mg/kg/day – target level 200-400 ng/mL) or TAC (0.3 mg/kg/day – target level 5-15 ng/mL) + MMF (100 mg/m2 b.i.d) and steroid. Formulation: not specified. Follow-up: median 35 months (range: 23–180)	N=16 (19 Txs conducted, but 3 patients died immediately after procedure). Mean age 4.7±2.3 years. Males:females=8:8	13 patients were alive (follow-up period: 23–180 months). 4 patients had at least 1 episode of chronic graft rejection. Two were managed with cortisone pulses and two required anti-thymocyte globulin. The only alterations in immunosuppression required were switches from CsA to TAC in 3 cases, and from TAC to CsA in one case. The authors comment that newer immunosuppressant agents such as MMF do not adversely affect renal function, and therefore it is possible to achieve immunosuppression using CNIs at doses that avoid side effects.	MMF maintenance regimen used in 13 living patients.
	Rationale for Classification of Evidence: This is a single-centre retrospective case review including MMF in maintenance.				
Martin et al. 2011	Observational study with long-term follow-up to compare outcomes following liver Tx for AIH to overall pediatric LTx population (non-AIH)	Dose: not specified. Formulation: not specified. Follow-up: 5-years.	AIH N=113 Age: 12.9±0.4 years (mean 14.2) Males:females=35%:65% Non-AIH N=1,411 Age: 6.7±0.1 years. (mean 4.8) Males:females=49%:51%	Initial immunosuppression in AIH vs. non-AIH patients (TAC based: 72.6% vs. 62.6%, p=0.045; MMF use: 31.0% vs. 21.6 %, p=0.02) and immunosuppression at 2 years post-Tx (monotherapy: 51.9% vs.17.3%, p<0.0001). MMF was used in a greater proportion of AIH patients than non-AIH from the time of Tx; over time, similar but small reductions in the use of MMF was reported in both groups. Late (>3 months), but not steroid-resistant or chronic rejection, was more common in AIH (log-rank p=0.0015). 5-year post-Tx survival for AIH was 86% (95% CI: 73 to 93). Study did not aim to compare immune-suppression regimens, but did demonstrate that standard regimens were effective following Tx in patients with AIH, although these patients required a higher degree of immunosuppression than patients transplanted for other indications.	Auto immune hepatitis Immunosuppressive regimens including MMF are effective in children who receive LTx as a result of AIH.
	Rationale for Classification of Evidence: This is a multi-centre observational study comparing outcomes in children with an underlying diagnosis of AIH with non AIH both of whom received MMF containing regimens.				

ABOi = blood group incompatible; AIH = autoimmune hepatitis; b.i.d. = twice a day; BPAR = biopsy-proven acute rejection; CI = confidence interval; CMV = cytomegalovirus; CNI = calcineurin inhibitor; CsA = ciclosporin A; EBV = Epstein-Barr virus; GFR = glomerular filtration rate; IH = isohemagglutinin; IVIG = intravenous immunoglobulin; LTx = liver transplant(ation); MMF = mycophenolate mofetil; OR = odds ratio; PTLD = post-transplant lymphoproliferative disorder; TAC = tacrolimus; Tx = transplant(ation).

Comparison and analyses of results across studies

Study populations

Paediatric Heart Transplant - Real World Data from Registries

The demographic characteristics of children receiving HTx in the US between 2007-2009 and 2017-2019 are provided from the OPTN/SRTR registry data and shown in **Table *29***. Across the two periods, the demographic baseline of HTx recipients has remained stable.

Table 29 Demographic Characteristics of Paediatric Heart Transplant Recipients, 2007-2009 and 2017-2019

Characteristics	N (%)	
	2007-2009	2017-2019
All recipients	1064 (100.00%)	1414 (100.00%)
Age		
<1 year	304 (28.6%)	364 (25.7%)
1-5 years	263 (24.7%)	336 (23.8%)
6-10 years	153 (14.4%)	195 (13.8%)
11-17 years	344 (32.3%)	519 (36.7%)
Sex		
Female	484 (45.4%)	625 (44.2%)
Male	580 (54.5%)	789 (55.8%)
Race/ethnicity		
White	567 (53.3%)	738 (52.2%)
Black	212 (19.9%)	280 (19.85%)
Hispanic	197 (18.5%)	284 (20.1%)
Asian	65 (6.1%)	69 (4.9%)
Other/unknown	23 (2.2%)	43 (3.0%)
Insurance		
Private	513 (48.2%)	548 (38.8%)
Medicaid	426 (40.0%)	733 (51.8%)
Other government	86 (8.1%)	96 (6.8%)
Unknown	39 (3.7%)	37 (2.6%)
Geography		
Metropolitan	897 (84.3%)	1142 (80.8%)
Non-metropolitan	167 (15.7%)	272 (19.2%)

Source: Colvin et al. 2021.

Published Literature

Most of the retrieved publications presented studies comparing the calcineurin inhibitor-azathioprine (CNI-AZA) containing immunosuppressive regimes to regimens containing MMF and evaluating the effect that switching AZA for MMF would have on the renal function, episodes of rejection, use of corticosteroids and overall survival post-transplant. Some studies have looked at the effects that ciclosporin A (CsA)-containing regimens have on the kidney function in paediatric HTx patients. When exposed to CsA post-transplant as part of the maintenance immunosuppressive regimen, some children develop nephrotoxicity and reduced renal function.

Boyer et al. (2005) showed an improvement in both glomerular and tubular renal functions in 14 children under the age of 17 treated with MMF. According to the MAH, reducing or discontinuing CsA dosage with

concomitant replacement of AZA by MMF is a safe way to improve renal function in children with HTx and CNI-induced nephrotoxicity (Boyer et al. 2005, Rosenthal et al. 2021).

Several studies have also looked into the effects of MMF on organ rejection in children under 17 years old with a HTx. Most of them seem to agree that switching from AZA to MMF as part of their maintenance immunosuppressive treatment has a significant and positive impact on the rejection episodes of these patients (Groetzner et al. 2005, Lammers et al. 2010, Lamour et al. 2019, Marshall et al. 2013), with one study indicating that MMF can even have a positive effect in the treatment of these events (Dipchand et al. 2001).

Chronic steroid usage can lead to complications such as stunted growth, hypertension, glucose intolerance/diabetes, hyperlipidemia, weight gain and osteoporosis. All these effects may affect long-term outcomes and quality of life of children. Steroid sparing is of particular interest in paediatric patients who will need immunosuppression for the rest of their lives, and also are undergoing growth.

Dipchand et al. (2001) showed that switching from AZA to MMF also facilitates steroid dose reduction, and the implementation of a steroid-free regimen in children under 17 years old. Other studies have shown that patients receiving MMF as part of their treatment can be managed safely with steroid avoidance immunosuppression regimens, with low rejection rates and good survival outcome (Lamour et al. 2019, Singh et al. 2010).

Cardiac allograft vasculopathy (CAV) is an important cause of graft failure in HTx recipients. One study looked at the effects of different immunosuppressive regimens in children under the age of 19 years old on the development of CAV. The use of MMF appeared to have a protective effect against the development of CAV in these patients (Moffett et al. 2014)

Paediatric Liver Transplant - Real World Data from the Registries

The demographic characteristics of children receiving LTx in the US between 2007-2009 and 2017-2019 are provided from the OPTN/SRTR registry data (see **Table 30**). Across the two periods, the demographic baseline of LTx recipients has remained stable.

Table 30 Demographic Characteristics of Paediatric Liver Transplant Recipients, 2007-2009 and 2017-2019

Characteristics	N (%)	
	2007-2009	2017-2019
All recipients	1790 (100.00%)	1713 (100.00%)
Age		
<1 year	542 (30.3%)	442 (25.8%)
1-5 years	692 (38.7%)	668 (39.0%)
6-10 years	232 (13.0%)	248 (14.5%)
11-17 years	324 (18.1%)	355 (20.7%)
Sex		
Female	892 (49.8%)	825 (48.2%)
Male	898 (50.2%)	888 (51.8%)
Race/ethnicity		
White	925 (51.7%)	861 (50.3%)
Black	321 (17.9%)	280 (16.3%)
Hispanic	387 (21.6%)	397 (23.2%)
Asian	118 (6.6%)	125 (7.3%)
Other/unknown	39 (2.2%)	50 (2.9%)
Insurance		
Private	797 (44.5%)	626 (36.5%)
Medicaid	15 (0.8%)	19 (1.1%)
Other government	120 (6.7%)	134 (7.8%)
Unknown	64 (3.6%)	84 (4.9%)
Geography		
Metropolitan	1439 (80.4%)	1403 (81.9%)
Non-metropolitan	351 (19.6%)	310 (18.1%)

Source: Kwong et al. 2021.

Published Literature

The majority of the retrieved publications presented studies that included children who had been exposed to CNI-based immunosuppressant regimens in the post-transplant period and subsequently developed nephrotoxicity and reduced renal function. Within this group of children, the studies evaluated the benefit of adding MMF to the regimen to enable CNI dose reduction or cessation, in order to preserve renal function. The endpoint is typically an improvement in renal function as measured by glomerular filtration rate (GFR), and balanced with the risk of rejection (Aw et al. 2001, Nobili et al. 2003, Ferraris et al. 2004, Evans et al. 2005, Tannuri et al. 2007). One study (Leiskau et al. 2018) evaluated the benefit of using a combination of TAC and MMF without the development of renal impairment or renal toxicity.

Three other studies provided information on the use of MMF containing regimens in children who received ABOi LTx. The children included in these studies were typically below 3 years of age and received MMF within an individualised and intensive immunosuppressive regimen typically incorporating plasmapheresis, immunoglobulin and B cell depleting agents in addition to agents such as CNI, antimetabolites and steroids. Graft and patient survival were used as evidence of benefit of the regimen,

and to show that this type of transplant is feasible (Schukfeh et al. 2015, Mysore et al. 2018, Dhungel et al. 2019).

The use of MMF in rescue for children with allograft rejection was evaluated in two retrospective studies (Chardot et al. 2001, Aw et al. 2008). The studies included children with steroid resistant rejection, or those who had received insufficient immunosuppression.

Steroid sparing is also particularly important for children who will need immunosuppression for the rest of their lives while undergoing growth. One study evaluated use of MMF in children under 18 years old with a LTx and initiating immunosuppression (Teisseyre et al. 2011).

Other studies presented evidence of the benefits of MMF when used in Chinese children receiving LTx (Shen et al. 2008), in children with an underlying diagnosis of autoimmune hepatitis (Martin et al. 2011), and in children who have received LTx and where MMF has been used as a maintenance treatment (Xinias et al. 2010).

Comparison of efficacy results of all studies

Paediatric Heart Transplant

Despite significant improvements in paediatric HTx outcomes, significant morbidity and mortality are still associated with it in the form of graft rejection, graft failure, infection, long-term corticosteroid use and other complications related to either under-immunosuppression or over-immunosuppression.

During the period of 1994-1999, the majority of paediatric HTx recipients were maintained on a triple therapy regimen with CsA, AZA, and prednisone. In contrast, during the period of 2001-2010, the most common regimen consisted of dual therapy with TAC and MMF, with most patients weaned off steroids (Marshall et al. 2013).

Currently, MMF has replaced the use of AZA in most centres (Singh et al. 2016), and is widely used as part of regular immunosuppressive regimens in clinical practice. One survey of several transplant centres in the United Kingdom (UK), Brazil, the US and Canada conducted by Castleberry et al. (2017) showed that a majority of the clinical protocols in those centres included MMF as long-term maintenance immunosuppression drug in paediatric HTx patients. MMF is also widely used in transplant centres in China as a routine component of the immunosuppressive treatment for paediatric HTx (Li et al. 2015).

Changes in immunosuppression regimens and the adoption of MMF have shown to be associated with improved 1-year, 5-years and 10-years survival in a 23-year retrospective, single-institution analysis of 180 paediatric and congenital patients by Tuite et al. (2021). These findings support the concept that advances in immunosuppressive strategies are associated with improved survival after HTx for paediatric and congenital cardiac disease, especially in high-risk cases (Tuite et al. 2021). These results are in line with the trends observed in the OPTN/SRTR registries.

Rejection

Despite improved immunosuppression, rejection accounts for significant morbidity and mortality in children after HTx.

Groetzner et al. (2005) reported that since the introduction of MMF to the immunosuppression protocols used in their centre in paediatric HTx patients, freedom from acute rejection after 5 years increased to 62%, compared to 40% with primary CsA immunosuppression regimen and 56% with TAC. It is also shown in this study that MMF in combination with CNI (started in 1995, n=27) led to a significantly higher freedom from acute rejection in the first year, compared to CNI combined with AZA or steroids (n=23; p=0.0013 from Kaplan-Meier analysis).

Lammers et al. (2010) reports the incidence and outcome of rejection of 105 children following HTx performed between January 2002 and August 2007. In this cohort, combination of MMF and TAC appeared to provide the best protective profile as the maintenance combination immunosuppressive therapy of choice, to prevent (hemodynamically relevant) rejection following orthotopic HTx in children. Of note, among the patients whose immunosuppression regimen contained MMF (n=50), none presented with a rejection resulting in hemodynamic collapse. The observed trend of a lower incidence of rejection with TAC and MMF than with TAC and AZA or TAC alone is in line with emerging data on MMF therapy in adults, and preliminary experience in children, as reported by other centres.

Marshall et al. (2013) performed a retrospective, historical-control, observational study comparing short-term outcomes in patients who received a classic CsA-AZA-steroid-based treatment regimen without induction, and those who were transplanted using a TAC-MMF-based steroid-sparing protocol with the use of cytolytic induction therapy. A total of 103 paediatric HTx patients who underwent primary HTx at the Morgan Stanley Children's Hospital of New York between 1 January 2005 and 31 May 2010 were included in the study. 64 patients were from the control group (undergoing transplant between January 2005 and Apr 2008), and 39 from the new protocol group (undergoing transplant between May 2008 and May 2010). The results showed that in the first year after transplantation, the proportion of patients with at least one episode of acute rejection was lower in the new protocol group compared to the control group (38% vs. 58%; odds ratio [OR] 0.41; 95% CI: 0.18 to 0.92, p=0.042). Also, patients that received treatment with the new protocol had a greater freedom from rejection time during the first year after the HTx than those in the control group (p=0.044). During the second year, the proportion of patients experiencing one episode of rejection was comparable in the two groups, 5% in the new protocol group vs. 4% in the control group.

Cardiac Allograft Vasculopathy (CAV)

CAV is an important cause of graft failure in HTx recipients. Moffett et al. (2014) performed a single centre, retrospective analysis on 148 patients aged under 19 years old who underwent HTx between 1996 and 2012, with the aim to identify the effect of the different immunosuppressive regimens on the development of CAV. Patients' medication regimens were followed for 1 of 3 endpoints: date of first CAV diagnosis, re-transplantation, or death. CAV was determined by angiography/imaging or pathology. The multivariate hazard model analyzing the time to CAV suggested that the use of MMF resulted in a decreased risk of developing CAV in paediatric HTx patients (hazard ratio [HR]=0.45, CI: 0.2, 0.98, p=0.04).

Renal Sparing

Safely improving renal function in HTx paediatric patients has become a major objective while handling immunosuppressive regimens in paediatric HTx patients.

Boyer et al. (2005) showed an improvement in both glomerular and tubular renal functions in 14 children with MMF following a dosage reduction of CNI (e.g., CsA). Both insulin and creatinine clearance increased significantly following the switch and this effect appears to be of rapid onset and long lasting. They concluded that reducing CsA dosage with concomitant replacement of AZA by MMF appears to be a safe way to improve renal function in children with HTx and CNI-induced nephrotoxicity.

CsA-discontinued immunosuppressive therapy can be safe in HTx patients with no increase in organ rejection or death, and leads to a significant recovery of kidney function (Rosenthal et al. 2021).

Steroid Sparing

Another goal of utilising MMF in paediatric HTx patients is to minimise corticosteroid exposure. As survival after HTx continues to improve in the paediatric population, the morbidity complications associated with long-term corticosteroid therapy such as stunted growth, hypertension, glucose intolerance/diabetes,

hyperlipidemia, weight gain and osteoporosis may affect long-term outcomes and quality of life in children. These metabolic side effects may be minimised by a "steroid-avoidance" approach to immunosuppression in paediatric HTx recipients.

Published literature on both heart and renal transplant show evidence that MMF may allow for lower doses or even elimination of corticosteroids from the immunosuppression regimens.

Dipchand et al. (2001) reported that it is possible to successfully reduce and/or discontinue corticosteroids in HTx paediatric patients, with successful discontinuation in 28% of patients on MMF, and ongoing dosage reduction in 20% of patients enrolled in their study (n=21).

Lamour et al. (2019) have shown that paediatric HTx recipients without donor specific antibodies at transplant and treated with a MMF containing regimen can safely avoid steroid treatment and have excellent short-term survival and low risk of first-year diabetes mellitus and post-transplant lymphoproliferative disorder (PTLD).

Singh et al. (2010) performed a single centre, retrospective analysis of 55 HTx patients that had entered a steroid-avoidance immunosuppression protocol consisting of thymoglobin induction, followed by a TAC-MMF, corticosteroid-free regimen. The primary outcome variable was freedom from moderate rejection (International Society for Heart and Lung Transplantation grade 2R/3A or antibody-mediated rejection). Median age was 7.2 years. Results showed that freedom from rejection was 92% at 6 months, and 87% at 1 year. Post-transplant survival was 91% at 6 months and 88% at 12 and 24 months. This demonstrates that an immunosuppression protocol consisting of induction treatment and followed by corticosteroid avoidance, and a TAC-MMF based regimen appears to achieve acceptable rejection rates during the first year post transplant in paediatric HTx recipients.

ABO-Incompatible Transplant

In a retrospective, multicentre analysis of 55 ABOi paediatric patients that underwent HTx, Urschel et al. (2013) concluded that successful ABOi HTx can be performed at an older age and with higher isohemagglutinin titers than initially assumed and using similar immunosuppressive regimens as for ABO-compatible transplants. Rejection and graft vasculopathy are rare. Sixty-two percent of the patients included in this study received MMF as part of their immunosuppression regime, along with CNI and low dose steroids. Furthermore, the authors concluded that given the lack of effective suppression of B-cell immunity by CNI, one could postulate that an anti-proliferative drug such as MMF should be a mandatory part of the regimen in ABOi HTx.

Paediatric Liver Transplant

Paediatric LTx is performed to treat acute and chronic liver failure due to any cause, in appropriately selected patients and without contraindications (e.g., only a few cases related to malignancy, terminal conditions, poor expected quality of outcome). In children, cholestatic biliary atresia is the most frequent cause of liver failure. Over the last decade, graft survival has improved. Acute cellular rejection is encountered in up to 60% of recipients within the first few years after liver transplantation and chronic rejection can be seen in as many as 10% of paediatric transplantation patients in some series (Yazigi 2013). Long-term use of corticosteroids and CNIs in paediatric LTx patients can lead to growth failure, renal impairment, dyslipidemia, hypertension, diabetes mellitus, and PTLD. Therefore, it could be beneficial to opt for short-term utilisation of these drugs in paediatric patients or use alternative immunosuppressant regimens containing, for example, MMF (Ruth et al. 2014).

Rejection

Chardot et al. (2001) published a preliminary, retrospective experience on the use of MMF as a rescue therapy in 19 children that underwent LTx. The median initial oral dose of MMF was 23 mg/kg/day (range: 12–43). In the earlier experience, the initial dose of MMF was extrapolated from the adult dose (2–3 g/day) to 40 mg/kg/day. With increasing experience, this initial dose was reduced to 20 mg/kg/day. No MMF assay was available during the period of the study, and MMF therapy was adapted according to clinical and biological tolerance. Median follow-up after initiation of MMF therapy was 642 days (range: 229–1606 days). MMF was indicated for rejection or insufficient immunosuppression in 16 cases, with normalisation of both liver function tests and liver histology in 10 cases (62%). MMF was successfully used in one patient with post-LTx immune hepatitis and one patient with corticosteroid dependence. In three patients with renal function impairment, MMF allowed reduction of CsA or TAC blood levels, without subsequent rejection.

Aw et al. (2008) evaluated the long-term outcomes of 26 children who received rescue therapy with MMF for steroid resistant rejection. The median age at transplant was 1.7 years (range: 0.4–13.6). Primary immunosuppression was CsA-based in 22 patients, and TAC-based in 6. All patients except one had been converted to TAC prior to MMF, having already received a median of 2 (1 to 5) courses of high-dose intravenous methylprednisolone. The median time to MMF rescue therapy was 1.8 months (range: 0.4–35.8). In 21 of the 28 episodes of steroid resistant rejections, patients responded to MMF therapy. MMF was added at a dose of 10 mg/kg/day in divided doses, and the dose was increased to a maximum of 40 mg/kg/day over 2 weeks (mycophenolic acid [MPA] assay tests were not available at the time). The median follow-up was 8.8 years (range: 7.7–11.5). In responders, there was 1 death from PTLD, and no grafts were lost due to chronic rejection. In the 7 non-responders, 3 grafts were lost due to chronic rejection, and 2 resulted in death. Surviving children were clinically well, with good liver function, and 17 remained on MMF.

Renal Sparing

LTx allows survival of children with end-stage liver disease; however, the need for immunosuppression is typically prolonged or life-long. Immunosuppressive regimens based on CNIs have had a positive impact on reducing rejection episodes. However, concerns exist related to the long-term impact on renal function by use of CNIs, as well as the risks of hypertension, neurological toxicity, cardiovascular risk, metabolic and cosmetic side effects. MMF has a different mechanism of action than CNIs and regimens using MMF alone or in combination have been studied in children with liver transplants. Based on the available evidence, MMF is frequently used as a part of renal sparing immunosuppression in the protocols of many transplant centres. The benefit of renal sparing is carefully balanced with the increased risk of opportunistic infection and neutropenia associated with MMF treatment.

Aw et al (2001) studied the use of MMF as a renal rescue to reduce the CNI exposure in 14 paediatric LTx recipients with CNI related nephrotoxicity. Patients had stable liver graft function and a glomerular filtration rate (GFR) $<$80 mL/min/1.73 m2. MMF was introduced at 20 mg/kg/day and increased to 40 mg/kg/day after one week. CNI dose was then reduced to achieve blood levels 25% of baseline. GFR was reassessed after 6 and 12 months. The median GFR increased from a baseline of 52 to 69 at 6 months and 73 mL/min/1.73m2 at 12 months, respectively ($p<0.001$). Side effects of MMF included decreased white cell count in two patients and backache in one. Two patients discontinued MMF. Acute allograft rejection occurred in three patients. All 14 patients were well at a median follow-up of 24 months from MMF introduction.

Nobili et al. (2003) reported on eight children that underwent paediatric LTx at least 5 years previously and had stable graft function with probable CNI induced renal dysfunction. CNI therapy was replaced by MMF in all patients. MMF was introduced at a dose of 20 mg/kg/day in two divided doses and increased to 40 mg/kg/day during the first month. TAC or CsA, at the same time, was reduced by 25% and

subsequently gradually reduced every 2 weeks to achieve blood levels 25% of baseline over a period of 2 months. Serum creatinine, uric acid concentration, azotemia and creatinine clearance before and 6 months after study entry were measured. The patients were monitored closely for adverse events of MMF as well as graft function. The mean serum creatinine values were 1.18 mg/dL at 6 months before MMF introduction, and 0.83 mg/dL at 6 months after MMF introduction (p=0.01). The mean uric acid concentration were 7.72 mg/dL at 6 months prior to MMF, and 5.66 mg/dL at the last follow-up (p=0.001). The mean BUN varied from 25.4 mg/dL at 6 months before MMF introduction to 18.80 mg/dL after 6 months of MMF treatment (p=0.005). Additionally, creatinine clearance had improved in all patients at the last follow-up. The mean values were 71.20 mL/min at 6 months before MMF introduction, and 88.40 mL/min at 6 months after MMF. The difference in creatinine clearance was not statistically significant. The AST and ALT concentrations were stable during the study period and no increase in serum bilirubin was observed. Only one patient reported temporary pruritus and nausea.

Ferraris et al. (2004) characterised the incidence of chronic renal dysfunction (n=52), and the effect of combining MMF and a reduced CsA dose on renal function (n=14) and immune response was evaluated five years after LTx. Fourteen patients developed chronic renal dysfunction (creatinine clearance <75 ml/min/1.73 m2) secondary to CsA toxicity as evaluated by renal biopsy. In 11 patients CsA dose was decreased to target levels 40–90 mg/mL with MMF 600 mg/m2 b.i.d. Plasma creatinine levels decreased (from 1.0±0.03 to 0.8±0.03 ng/dL, p<0.007), creatinine clearance increased (from 66.8±3.0 to 99.2±6.3 mL/min/1.73 m2 , p<0.002), and microalbuminuria decreased (from 21.0±8.6 to 3.6±1.1 mg/24 h, p<0.05) after 12 months of MMF therapy combined with reduced CsA. MMF allowed the reduction of CsA, with an improvement in renal function, no risk of rejection, and minor changes in the immune response.

In a retrospective analysis, Evans et al. (2005) evaluated the long-term use of MMF in children who received the drug as a result of renal dysfunction (calculated glomerular filtration rate [cGFR]<65 mL/min/1.73 m2) after orthotopic LTx. Forty-eight children began MMF at a median age of 11.1 years (range: 0.9–18.1) and at a median of 4.0 years (range: 0.3–12.4) post-LTx. Median baseline cGFR was 54 mL/min/1.73 m2 (range: 29–65). Immunosuppression after transfer was MMF monotherapy in 36 children, MMF with steroids, in 4 children and MMF with low-dose CsA or TAC in 8 children. Twenty-three children were transferred to MMF monotherapy by introducing MMF at 20 mg/kg per day in two divided doses and at the same time, halving the CsA dose. After 2 weeks, CsA was discontinued as long as liver biochemistry and a full blood count were normal. The remaining 13 children were transferred to MMF in the same way, but prednisone at a dose of 5 mg/day was added to their therapy temporarily for 3 months to prevent liver-allograft rejection. This was then reduced and discontinued, leaving the patients on MMF monotherapy. For those receiving CsA or TAC with prednisone, MMF was simply added to the regime at a dose of 20 mg/kg per day in two divided doses and after 2 weeks, if liver biochemistry was stable, the CsA or TAC dose was reduced to give low levels of 40–60 μg/L or 3–5 ng/mL, respectively. The same approach was used for those receiving CsA in combination with AZA, except that AZA was discontinued when MMF was introduced. In all cases, MMF was increased to a maximum of 40 mg/kg per day in two divided doses if renal dysfunction had not improved by 3 months after transfer to MMF. In 44 patients (92%) there was a statistically significant increase to a median cGFR of 69 mL/min/1.73 m2 (range: 28-114) by 1 month and a further increase to a median cGFR of 77 mL/min/1.73 m2 (range: 24–105) by 2 months of MMF treatment, after which cGFR levels were maintained. Children aged less than 3 years at LTx or who were less than 5 years post-LTx, when MMF was introduced, demonstrated greater increases in cGFR. Four children with a median baseline cGFR of 34 mL/min/1.73 m2 (range: 31–49) did not respond and progressed to end stage renal failure. Liver function abnormalities occurred in seven children (15%): transient transaminitis in three, acute rejection in two, and chronic rejection in two of whom one required re-transplantation.

Tannuri et al. (2021) retrospectively evaluated the efficacy and safety of the long-term use of MMF with reduced doses of CNIs. Out of 191 paediatric LTx recipients, 11 children developed renal dysfunction

secondary to prolonged use of CsA or TAC, 1-12 years post-LTx. MMF was introduced at an initial twice-daily dose of 10 mg/kg and increased gradually to 40 mg/kg/day within a two-week interval. After introduction of MMF, the CNI dosage was reduced gradually to 50% of baseline dosage over a period of one month, without concern for drug levels. Renal function improved in 9 of 11 patients (82%). There were no episodes of acute or chronic rejection or increased infection rates during the 24-month study period. Two patients developed transitory diarrhea and leukopenia that recovered with reduction of MMF dosage to 30 mg/kg/day.

A single study was identified where the effectiveness and safety of de novo MMF and TAC-based regimens (n=19) were compared to retrospectively age and diagnosis matched cohorts treated with TAC monotherapy (n=19) or CsA and prednisolone (n=19; Leiskau et al. 2018). TAC reduction in combination therapy (0.7 μg/L over the year) was lower than targeted (2 μg/L). Biopsy proven acute rejection occurred equally in MMF/TAC and TAC groups (31.6% each), being slightly higher in CsA group (42.1%; OR=1.5; 95% CI: 0.42 to 5.44; p=0.5). GFR deteriorated comparably in all 3 groups ($p<0.01$ each), without significant differences between the groups.

Steroid Sparing

An abstract of a study was identified publishing the three year follow up of a study comparing immunosuppression with TAC, with or without MMF for early steroid withdrawal in children after LTx (Teisseyre et al. 2011). Group A included 22 patients aged 0.2–18 years treated with TAC and MMF, group B included 22 patients aged 0.12-18.1 years treated with TAC and steroids. MMF was administered from 0-90 days and then reduced and discontinued finally 4 months after LTx. In group B, steroids were administered according to a low-dose scheme and at the end of month 7 steroid withdrawal was started. The incidence of acute rejections, liver and renal function, serum glucose, blood pressure, frequency of viral infections and liver biopsy: 0-6 months, 1, 2, and 3 years after LTx were evaluated. Liver and renal function, blood glucose and incidence of cytomegalovirus infections were similar in both groups 1, 2 and 3 years after LTx. Patients in Group A showed a reduced need for antihypertensive treatment ($p<0.05$) in the early post-transplant period and 1 and 2 yrs post transplantation. A reduced incidence of Epstein-Barr virus infection was observed in Group A without steroids in 1, 2 and 3 years after LTx ($p<0.05$). Acute rejection episodes were more frequently recognised in Group A in the second year post LTx ($p<0.05$). Steroid resistant acute rejection was not observed in either group. More patients from group A showed normal liver histology one year post LTx however this difference was not significant.

ABO-Incompatible Transplant

ABOi transplant has been performed primarily in children and typically in urgent cases as a way to address the scarcity of donor organs. The liver is viewed as an organ with greater resistance to acute rejection than the kidney or heart and was initially the organ where ABOi transplant was more frequent (Starzl et al. 1982, Demetris et al. 1988). Early trials showed poor graft survival due to antibody mediated rejection. Subsequently many approaches have been implemented to reduce the risk with the primary goal being reduction of ABO antibodies and suppression of B cell activity. Plasmapheresis, splenectomy, intravenous immunoglobulin, intrahepatic portal and arterial infusion, anti-lymphocyte antibodies, B cell depleting agents and enhanced immunosuppression represent some of the methods used to increase the success of ABOi transplant.

Three studies were identified where ABOi liver transplants were performed and MMF was part of the immunosuppressive regimen.

Schukfeh et al. (2015) published a prospective analysis of six paediatric ABOi LTx recipients under 3 years of age, matched with six patients receiving ABO-compatible transplant comparable in the recipient's preoperative paediatric end-stage liver disease (PELD), age, gender and the technical aspects of transplant and receiving transplant in the same period. At the time, there was experience of ABOi LTx

from Asian countries with good outcomes, but the procedure was rarely performed in Europe. The median follow-up was 2.6 years (range: 1–4.5). At the time of operation, the mean body weight was 7.7 kg (range: 5.7–16 kg) in ABO-compatible LTx recipients and 8.8 kg (range: 5.5–18 kg) in ABOi LTx recipients. In each group, the median PELD score was 28 (range: 28–35). The postoperative immunosuppressive regimen consisted of intravenous or oral prednisolone (initially 15 mg/m2 body surface area [BSA] at days 1–10 postoperatively), TAC (from 2 x 0.05 to 0.1 mg/kg) orally, and MMF (2×10mg/m2 BSA). MMF was introduced orally at Day 3, and four ABOi transplanted patients received intravenous immunoglobulins at Days 1, 3, and 5 after liver transplantation. Patient and graft survival in this group was 83%. One female patient died within 24 hours due to fulminant gram-negative sepsis. Another patient developed acute cellular rejection at the Day 8 postoperative, which responded to steroid treatment. No further complications occurred. In the ABO-compatible group, patient survival was 100% and graft survival was 83%; one patient in this group received re-transplantation after 4 days. During follow-up, two patients of the ABOi group had maximum alloantibody titers of four against the donor's blood group; all other patients had titers below four.

Mysore et al. (2018) developed and implemented a novel immunosuppression protocol in their Texas-based centre specifically for children undergoing ABOi LTx and based on quantification of isohemagglutinin (IH) titres. Children with high pre-transplant IH titers (≥1:32) underwent an enhanced immunosuppression protocol including plasmapheresis, rituximab, IVIG, and MMF (15 mg/kg/dose b.i.d.), while children with IH titers ≤1:16 received steroids and TAC. Outcomes of ABOi LTx with ABO-compatible recipients of similar age and diagnosis over a 2-year period were retrospectively compared. Ten children with median age of 8.9 months underwent ABOi LTx, 4/10 patients underwent enhanced immunosuppression due to high IH titers. Rates of complications (rejection, infections, biliary and vascular) at both 1 year and up to 3 years post-transplant were comparable between the groups. Patients with ABOi LTx had good graft function with 100% survival at a median follow up of 3.3 years.

A further abstract was identified in which 8 cases of patients receiving ABOi LTx were described where immunosuppression with MMF was started 1 week before transplant as part of the regimen and continued as part of triple therapy post operatively (no dose details given). Patient and graft survival was 100% in recipients at a mean follow-up of 33 months (range: 2–80; Dhungel et al. 2019).

Comparison of results in subpopulations

The retrieved publications include studies that offer limited information on the comparison of outcomes in different subpopulations. The information available from OPTN/SRTR registries provides some evidence related to outcomes in different subpopulations, though this cannot be directly and/or solely attributed to a particular MMF regimen or dosage.

Paediatric Heart Transplant

Real World Data from the Registries

Age

Overall, the rate of acute rejection at 1 year post transplant for transplants between 2017-2018 was similar for all age groups at approximately 20%. Five-year patient survival for transplants between 2012-2014 was similar for all groups ranging from 81.3% for recipients aged younger than 1 year to 85.4% for ages 11–17 years.

Sex

No information is published specific to outcome and patient survival for paediatric HTx recipients by sex. However, for adults, the data for males and females overlay each other and suggest that survival is not impacted by sex.

Paediatric Liver Transplant

Real World Data from the OPTN/SRTR Registries

Age

Across age groups, the incidence rate ranges from 21.3% in recipients aged younger than 1 year to 29.4% in those aged 1-5 years. There was little variation by age in the 5-year graft survival rates ranging from 81.1% for recipients aged younger than 1 year to 85.5% for ages 11-17 years.

Sex

No information is published specific to outcome for paediatric or adult LTx recipients by sex. The registry data do confirm that the paediatric candidates wait-listed for LTx have consistently followed an equal distribution with respect to sex since 2008.

Living-Donor Recipients vs Deceased-Donor Recipients

Paediatric living-donor transplant recipients show a reduced rate of graft failure compared with deceased-donor transplants that is apparent from approximately one year after transplant and most evident at ten years post-transplant where deceased-donor recipients have a failure rate of 24.8% and living-donor recipients have a failure rate of 17.6%.

2.4.3. Discussion on clinical efficacy

The off-label use of MMF-containing regimens in paediatric heart and liver transplant recipients has increased over time. These regimens are broadly aligned with the use patterns in adults, although the benefit of steroid and CNI sparing may be more important for paediatric patients who are undergoing growth and who have a need to preserve renal function for a longer time compared with adults.

In graft survival for heart and liver, and patient survival for heart and liver transplant, the efficacy of MMF is comparable with that observed in adults, although paediatric patients tend to have better outcomes relative to adults, particularly at time points beyond the first year post-transplant.

The MAH proposes to extend the current indication of MMF to allow paediatric patients access to the medicine.

No new dose-response trials were conducted in paediatric patients. The mechanism of action of MMF (conversion of the mycophenolate prodrug MMF into its active moiety MPA, which then inhibits IMPDH resulting in a decreased lymphocyte proliferation) is independent of transplant type. Exposure to MPA is determined by measuring the conversion of MMF to MPA and by MPA's metabolism to its inactive 7-O-glucuronide MPAG. This is also independent of patient age.

When expanding indications for CellCept from the RTx indication in adults to other transplant types in adults (heart, liver) and to RTx in children, it was assumed that similar systemic exposure to MPA will yield comparable efficacy independent of transplanted organ and age. This has been accepted by the CHMP.

The MAH also demonstrated that the pharmacokinetics of MPA show high inter-patient variability in general, even higher in paediatric than in adult patients, in liver and heart transplant than in renal transplant patients and early after transplantation than later. It was thus supported that in order to secure adequacy of immunosuppression, individual dosing, was needed (see section 4.2 of the SmPC).

The MAH also provided evidence that often higher doses than 600 mg/m2 are needed to achieve the target exposure (29 h • mg/L in the early or 58 h • mg/L in the late post-transplantation period) that has been shown to be effective in adults and more pronounced for heart and liver than for renal patients. Thus it is accepted that a higher maintenance dose than currently recommended might be needed for HTx and LTx.

The clinical efficacy data provided supporting the application originate from available publications of studies conducted in the paediatric population, including 14 studies relevant to paediatric heart transplant (HTx) and 15 studies relevant to paediatric liver transplant (LTx) patients.

In addition, clinical efficacy data from the Roche-sponsored pivotal trials conducted in the adult population, and data extracted from the Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR) Registries for HTx and LTx in the United States (US) are also included to provide the context for interpretation of the available literature data.

However, as pointed out by the MAH, the published studies are largely observational over a period of time, too small in sample size, and not designed to demonstrate the efficacy of MMF. They typically include MMF together with other therapeutic agents as a part of the immunosuppressive regimen, and it is therefore not possible to directly link or attribute any of the observed outcomes to MMF.

Furthermore, very few of the publications retrieved were prospective studies; most studies were retrospective comparisons of transplant outcomes in the years before the introduction of MMF versus outcomes in the years after the inclusion of MMF in standard of care immunosuppressive regimens. Therefore, although the studies consistently show a benefit for MMF, the impact of improved surgical and medical management is also likely to have influenced these findings.

Despite all these limitations, the results from the retrieved published studies suggest that as in adults, regimens containing MMF are effective in paediatric patients, with benefits of reducing the incidence of acute rejection and allowing calcineurin inhibitor (CNI) and steroid dose reduction. In addition, treatment with regimens containing MMF may improve the results of blood group incompatible (ABOi) transplantation.

However, all these additional data are only supportive. Since extrapolation from adults to children has been demonstrated, clinical efficacy is considered demonstrated.

2.4.4. Conclusions on the clinical efficacy

The available evidence suggests that regimens containing MMF are effective in paediatric patients. It is anticipated that the effect of immunosuppression with MMF is independent of type of solid organ transplantation and the efficacy is considered acceptable for paediatric RTx, HTx and LTx recipients in the following indication:

CellCept is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adult and paediatric (1 to 18 years of age) patients receiving allogeneic renal, cardiac or hepatic transplants.

2.5. Clinical safety

Introduction

No company-sponsored pivotal clinical trials were conducted to support the safety of MMF in the prophylaxis of organ rejection in paediatric recipients of allogeneic heart or liver transplants.

A Phase IV study evaluating the safety, tolerability and pharmacokinetics of oral MMF in paediatric liver transplant (LTx) recipients on concomitant treatment with ciclosporin A (CsA) and corticosteroids was conducted by the MAH between 2003 and 2005 (Study PA16497).

The majority of safety data supporting this application originate from available publications of studies conducted in the paediatric population, including 17 clinical studies relevant to paediatric heart transplant (HTx) and 26 studies relevant to paediatric LTx patients.

In addition, an analysis of cumulative post-marketing safety data was also conducted to compare the proportions of adverse events (AEs) reported in paediatric HTx or LTx patients with the proportions of AEs reported in adult HTx or LTx patients, respectively. For paediatric patients, the proportions of AEs reported in patients with HTx or LTx (i.e., off-label use) were also compared with the proportion of AEs reported in patients with RTx (i.e., on-label use).

All the data presented should be interpreted with caution, bearing in mind the limitations of the underlying assumptions. In addition, post-marketing reports are voluntary and subject to under-reporting and reporting biases, which further limit the strength of the resulting evidence. Bearing in mind these caveats, the overall safety profile from these comparisons appears largely similar to the safety profile established in non-paediatric patients and paediatric RTx recipients. No new safety signal in paediatric patients with HTx or LTx emerged from this analysis. There are a few imbalances presented and discussed.

Study PA16497

Part I of Study PA16497 was an open-label, multi-centre, non-controlled study that aimed to estimate the dose predicted to achieve an exposure of 58 µg.h/mL in stable paediatric hepatic transplant patients. The objective of part I of the study was to estimate the dose predicted to achieve an exposure of 58 µg.h/mL in stable paediatric hepatic transplant patients. The study planned to enroll 12 patients who would be dosed with MMF per center practice, not 600 mg/m2. Paediatric transplant recipients aged 9 months to 12 years of age, inclusive, who had received a first liver allograft from a cadaveric or living donor were targeted. Patients were enrolled for the time required for PK sampling and then contacted 14-16 days after sampling for adverse events.

However, the study was terminated early due to challenges with subject recruitment (e.g., only 35 patients were screened, and 9 patients were enrolled into Part I of the study between August 2002 and December 2004, infrequent use of the combination of triple therapy with MMF, CsA and steroids, etc.).

Table 31 Summary of Demographic Data (All Patients)

dm11_a1 Summary of Demographic Data by Trial Treatment
Demographic Data (All Patients)
Protocol(s): J16497A
Analysis: ALL PATIENTS Center: ALL CENTERS

	CellCept N = 9
Sex	
MALE	4
FEMALE	5
n	9
Age in years	
Mean	1.3
SD	1.50
SEM	0.50
Median	1.0
Min-Max	0 - 5
n	9
Weight in kg	
Mean	10.97
SD	2.220
SEM	0.740
Median	10.50
Min-Max	8.0 - 14.5
n	9
Height in cm	
Mean	77.674
SD	5.8522
SEM	1.9507
Median	76.000
Min-Max	71.12 - 86.36
n	9
Age (months) at Screening	
Mean	20.6
SD	15.46
SEM	5.15
Median	17.0
Min-Max	9 - 60
n	9
Race	
BLACK	1
CAUCASIAN/WHITE	5
HISPANIC	1
MIDDLE EAST EGYPTIAN	1
ORIENTAL	1
n	9
Body surface area in sqm	
Mean	0.487
SD	0.0675
SEM	0.0225
Median	0.470
Min-Max	0.40 - 0.59
n	9

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
DM11 10MAY2005:16:13:19 (PDRD)

Exposure: Nine paediatric patients were enrolled in Study PA16497. All patients received MMF twice a day (b.i.d.) at stable doses per centre practice (not 600 mg/m2) for at least 7 days prior to pharmacokinetic sampling. Mean MMF dose/m2 was 285 (81.1) mg/m2, with a range of 202 – 424 mg/m2. The mean MMF dose/kg was 12.9 (3.32) mg/kg and the range was 8.47 – 17.2 mg/kg.

Table 32 Actual CellCept Dose Expressed as mg, mg/m^2 and mg/kg

Patient	Age (months)	Weight (kg)	Height (cm)	BSA (m^2)	Actual Dose (mg)	Dose/m^2 (mg/m^2)	Dose/kg (mg/kg)
[redacted]	18	10.0	76.20	0.460	140	304	14.0
	24	14.5	85.00	0.590	250	424	17.2
	17	10.5	73.00	0.460	170	370	16.2
	9	8.1	71.12	0.400	90	225	11.1
	60	11.6	86.36	0.530	125	236	10.8
	10	8.0	72.39	0.400	125	313	15.6
	14	11.8	75.00	0.500	100	200	8.47
	15	10.5	76.00	0.470	100	213	9.52
Mean	20.9	10.6	76.9	0.476	138	285	12.9
SD	16.5	2.11	5.72	0.064	52.2	81.1	3.32
CV%	79.0	19.8	7.4	13.4	38.0	28.4	25.8
Median	16.0	10.5	75.5	0.465	125	270	12.6
Min	9.0	8.00	71.1	0.400	90.0	200	8.47
Max	60.0	14.5	86.4	0.590	250	424	17.2
Geometric Mean	17.4	10.4	76.7	0.473	130	276	12.5

Safety Results: One subject reported one adverse event (pyrexia) during the course of the study. This adverse event was mild in intensity and was assessed by the investigator as unrelated to trial treatment. There were no serious adverse events, no deaths or adverse events that led to the withdrawal of a patient recorded during the study.

Conclusions: Based on the assumptions that MPA exhibits linear PK, that an AUC achieved ≥ 6 months post-transplant is two-fold higher than an AUC in the immediate post-transplant period on the same dose of MMF, and an AUC of 29 µg.h/mL provides effective immunosuppression in the immediate post-transplant period, a dose of 740 – 806 mg/m2 would be required in the early post-transplant period to achieve adequate immunosuppression.

Published Literature Studies

A search of all published scientific literature in standard databases (Medline, EmBase, BIOSIS Previews and Derwent Drug File) was conducted to include data up until 31 December 2022. All publications with a minimum of 10 paediatric patients and providing substantive safety information related to MMF therapy were presented. The majority of the retrieved articles did not provide exact details on patient age (and other demographic characteristics), number of patients exposed to MMF, or length of exposure. Safety data and AEs reported in these articles could not always be linked to specific patients or treatment regimen.

Paediatric HTx: From the systematic literature search, 366 publications of studies in paediatric HTx were retrieved and ranked according to decreasing strength of evidence. Of these 366 publications, 17 were selected based on the above-mentioned criteria and are presented (see **Table 33**):

- Prospective studies: 3 publications (at least 63 HTx patients on MMF)
- Retrospective studies: 8 publications (at least 6,559 HTx patients on MMF)

- Conference abstract: 5 publications (at least 101 HTx patients on MMF)
- Consensus statement: 1 publication

Little data are available in terms of the duration of treatment, the dose and formulation of MMF. Where reported, MMF was used at a dose of 250 mg/day (Groetzner et al. 2005), 1,200 mg/m2 (Singh et al. 2010), 596 ± 99 mg/m2 (Siddiqi et al. 2015), titration to maximum 40 ± 14 mg/kg (Dipchand et al. 2001), or 600 mg/m2/dose b.i.d. to a maximum of 2,000 mg/day (Singh et al. 2016).

Paediatric LTx: From the systematic literature search, 806 publications of studies in paediatric LTx were retrieved and ranked according to decreasing strength of evidence. Of these 806 publications, 26 were selected based on the above-mentioned criteria and are presented (see **Table 34**):

- Prospective studies: 2 publications (44 LTx patients on MMF)
- Retrospective studies: 15 publications (at least 627 LTx patients on MMF)
- Conference abstracts: 9 publications (at least 459 LTx patients on MMF)

Little data are available in terms of the duration of treatment, the dose and formulation of MMF. Where reported, MMF was mostly used at a dose of 10-20 mg/kg b.i.d; Lightdale et al. 1997, Chardot et al. 2001, Evans et al. 2005, Aw et al. 2008, Leiskau et al. 2018, Ozturk et al. 2019, Renz et al. 1999, Tannuri et al. 2007, Honda et al. 2018, Nayagam et al. 2022. Ferraris et al. (2004) based their dosing regimen on body surface area (600 mg/m2 b.i.d).

Table 33 Summary of Paediatric Heart Transplant Studies Contributing to Safety Evaluation

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
Prospective				
Fine et al. 2021	Heart transplant recipients between 10 and 21 years of age and >1 year post-transplantation were recruited at the time of clinically indicated invasive coronary angiography or within 6 months of invasive angiography to undergo real-time myocardial contrast echocardiography (RTMCE) examination. Comparator arm: Yes	Dose and formulation of MMF not reported.	N=36; 18 received MMF Mean age: 13.5 ± 4.3 years; Male:females=21:15	3/18 patients on MMF had CAV by ICA (compared to 5/36 from the whole cohort)
	Rationale for classification of evidence: This is a prospective two-centre study in a small sample size on MMF (<50) with a primary objective to detect CAV in paediatric heart transplant recipients.			
Schubert et al. 2008	Prospective, single-centre, observational study monitoring immunosuppression and EBV load measurement using quantitative real-time PCR during January 2001 to December 2006 (5 years 11 months). Comparator arm: Yes	MMF-CsA (N=17) CsA-AZA (N=11) CsA-Eve (N=9) CsA only (N=4) Dose and formulation of MMF not reported.	N=41; 17 received MMF. Age: 7.2 months – 19.3 years (median age: 8.1 years). Males:females=16:25.	1/17 patients (5.8%) on MMF and CsA, 2/11 patients (18.2%) on CsA-AZA and 1/ 9 patients (11.1%) on CsA-Eve developed PTLD. EBV load was significantly increased in patients with CsA–AZA in comparison to patients with CsA–MMF and CsA only. Patients with CsA–Eve had an elevated EBV load as compared with CsA-MMF, which was not statistically significant. EBV load decreased in 6 patients in whom AZA was ceased and changed to CsA–Eve a 1-year follow-up, without occurrence of PTLD.
	Rationale for classification of evidence: This is a prospective, single-centre, observational study monitoring immunosuppression and EBV load measurement in a small sample size on MMF (<50).			

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
Jacobsen et al. 2018	Prospective longitudinal cohort study of children undergoing HTx for 1-year post Tx. Comparator arm: No	All patients were induced with basiliximab and IV steroids. Maintenance therapy was with TAC and MMF with oral steroids weaned by 6 months. Dose and formulation of MMF not reported.	N=28; all 28 received MMF. Age: 5 months to 16 years. Gender not specified.	7/28 patients (25%) had CMV DNA detection within first 12 weeks post-Tx.
	Rationale for classification of evidence: This is a prospective single-centre study with a primary objective to determine specific immunity to CMV in a small sample size (<50) paediatric cardiac transplant recipients on MMF.			
Retrospective				
Dipchand et al. 2001	Retrospective report on MMF experience in 21 pediatric heart transplant recipients to evaluate MMF as effective agent for the treatment of both established rejection and primary rejection prophylaxis in solid-organ transplantation (Tx).	Average MMF dose 40±14 mg/kg Formulation not provided	N=21; all patients on MMF Age: 12.3 years (range 11 months to 16.9 years). Age at Tx: 10.7 years (55 days to 16.7 years).	AEs reported in 38% of the patients: diarrhoea, 10%; gastrointestinal discomfort, 20%; leukopenia, 20%. Dose reduction or temporary discontinuation was required in 63% of the patients who experienced side-effects (24% of the total number of patients). Opportunistic infections developed in 10% (cryptococcus, CMV). MMF appears to be effective for treatment of rejection in the pediatric heart transplant population and has an acceptable safety profile. In addition, it may have a role in primary rejection prophylaxis and may facilitate a reduced steroid dosage or a steroid-free immunosuppression regimen.
	Rationale for classification of evidence: This study is a rejection-focused, small sample (<50), single-centre, retrospective chart review.			
Dipchand et al. 2022	Retrospective, single-centre, observational study monitoring early experience with live-attenuated varicella vaccine in a cohort of 31 children following heart transplantation	Tacrolimus-MMF (N=13) Sirolimus-MMF (N=1)	N=31; 14 received MMF Age: 2.4 weeks–5.9 years (median age at transplant 8.64 months). Age at vaccination 3.17-17.93 (median age at vaccination 11.7 years). Males:females=13:18	13/31 patients (41.9%) on MMF and tacrolimus and 1/31 (3.2%) on MMF and sirolimus. No major adverse events; rash was reported in 29% (of 31), spots were few and self-resolving in 1 to 3 days. The patients on MMF experienced minimal adverse events as described, providing early evidence that children on MMF can be eligible for vaccine.

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
	Rationale for classification of evidence: This is a retrospective, small sample (<50), single-centre, observational study specifically focused on varicella vaccine experience following heart transplantation.			
Giuliano et al. 2022	The United Network for Organ Sharing database was queried for pediatric (<18 years) heart transplant recipients from October 1987 through November 2019. Freedom from malignancy after transplant was assessed with Kaplan-Meier analysis. Cox regression was performed to generate hazard ratios (HRs) and 95% CIs for risk of malignancy development.	MMF nearly always used in combination with other agents. Dose and formulation of MMF not reported.	N=8,581, of whom 5.2% (n = 444) were repeat transplants and 0.7% (n = 63) were multiorgan recipients. On MMF >65% Average age at Tx 6.7 (SD, 6.2) years, Males:females=4,781:3,800	3,818 patients in the cohort had known recipient and donor Cytomegalovirus and EBV statuses. Malignancy developed in 8.1% of the whole cohort (86.4% PTLD). On multivariable analysis, MMF was associated with reduced risk of malignancy, a finding that has been reported in adult heart transplant patients. MMF is nearly always used in combination with other agents, but this does support the safe addition of MMF to a regimen.
	Rationale for classification of evidence: This is a retrospective large-sized (>100) study to examine the incidence and risk factors for posttransplant malignancy.			
Groetzner et al. 2005	Retrospective analysis of clinical outcome of paediatric HTx patients between 1988 and 2002 (14 years). Comparator arm: No	The majority of patients (35 of 47; 74%) received CsA as primary immunosuppression regimen. Over time, after introduction of TAC, a growing number of patients received TAC (12 of 47; 26%). Long-term immunosuppression consisted of CNI and AZA (11; 25%) or MMF (33; 75%). MMF administered intravenously (250 mg/day) on the first postoperative days and continued orally after extubation. Target trough levels were 2–4 mg/L for MPA in the first year.	N=47; 33 received MMF. Age: 4 days to 17.9 years. Gender not specified.	MMF was associated with severe gastrointestinal side effects in 4/33 patients (12.1 %) necessitating a switch to AZA. 5 years-freedom from acute rejection improved significantly when CNI were administered in combination with MMF as a secondary immunosuppressant (40% with primary ciclosporin immunosuppression regimen, 56% with TAC and 62% with MMF). Among the 47 total patients, three patients died due to primary graft failure and therapy details were not available.
	Rationale for classification of evidence: This study is a single-centre, retrospective review providing freedom of rejection data for a small sample of patients on MMF (<50).			

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
Marshall et al. 2013	Retrospective, observational study comparing short-term outcomes in patients who received a CsA-AZA-steroid–based protocol without induction, and those who were transplanted using a TAC-MMF–based steroid-sparing protocol with the use of cytolytic induction therapy between 1 January 2005 and 31 May 2010 (5 years 5 months). Comparator arm: Yes	Study group: TAC+MMF; n=39 Control Group: CsA+AZA+Steroids; n=64 Dose and formulation of MMF not reported.	N=103; 39 received MMF. Age: 7.8±6.7 years. Gender not specified.	Mortality within the first year after Tx occurred in 8/64 patients (13%) in the control group compared with only 1/39 patients (3%) in the study group (TAC+MMF). Patients in both groups experienced similar rates of bacterial, fungal, and viral infections (EBV infection, CMV infection) within the first 12 months after transplant. Anaemia (51% vs 14%) and neutropenia (18% vs 5%) were more commonly seen in the study group compared to control group. There was no difference in the frequency of thrombocytopenia between the two groups (OR=1.1, 95% CI: 0.3 to 4, p>0.9).
	Rationale for Classification of Evidence: This is a retrospective observational, small sample (<50) single-centre study using a historical control which compared outcomes of two different combination treatments.			
Siddiqi et al. 2015	Retrospective analysis to assess the outcomes targeting MPA-trough level of 0.8–2.0 µg/mL in paediatric HTx collected 2–12 months, post-transplant. Comparator arm: No	Mean MMF dose was 596±99 mg/m^2.	N=22; all 22 received MMF. Age: 4.8 months – 19 years (median age: 2.5 years). Males:females=12:not reported.	Of the 22 patients exposed to MMF, adverse events reported with its use were leukopenia (WBC count <3000 cells/µL; n=13), gastro-intestinal events (n=3), bacterial pneumonia (n=1), and acute rejection requiring treatment with steroids (n=1). MMF was discontinued in two patients for leukopenia, and one patient was switched from MMF to AZA for gastrointestinal complaints with subsequent resolution of gastrointestinal symptoms.
	Rationale for Classification of Evidence: This is a small (<50), retrospective study to assess effect of MMF dose and trough levels on adverse effects in pediatric heart transplant recipients.			

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
Singh et al. 2010	Retrospective analysis of clinical outcomes in a cohort of paediatric HTx recipients managed using a steroid-avoidance protocol during the study period (2005–2009; 4 years). Comparator arm: No	Rabbit anti thymocyte globulin and methylprednisolone for 5 days followed by TAC+MMF (1,200 mg/m^2). Formulation not reported. MMF dosage was adjusted to achieve a target trough level of 2–4 mg/dL.	N=55; all 55 received MMF. Age: 2 weeks to 22 years (median age: 7.1 years). Males:females=27:28	Adverse events reported were: CMV antigenemia in 11 patients (20%), EBV viremia in 8 patients (14.5%), insulin-dependent diabetes mellitus in 1 patient (1.8%) and transient glucose intolerance in 1 patient (1.8%). There were 6 deaths, 5 of which were early hospital deaths in the post-Tx period due to multiple-organ failure. Patients with diabetes mellitus and transient glucose intolerance had family history of diabetes.
	Rationale for Classification of Evidence: This is a medium-sized (50-100) two-centre retrospective study evaluating the potential of MMF containing regimens to enable steroid sparing.			
Singh et al. 2022	An overview of the infant recipient and donor characteristics over time with an analysis of >3,500 infant heart trans-plants	Dose and formulation of MMF not reported.	N>3,500; on MMF >1,250 (≈70% in the period 2005-2009 and 91% in the period 2009-2018) Age <1 year (Infants) Gender ratio not provided	Mycophenolate mofetil was the preferred antimetabolite agent, used in 91% of infants transplanted during 2010-2018 at discharge. Freedom from PTLD was 98.8% at 1 year, 95.3% at 5 years, and 88.4% at 10 years post-transplant in infant heart transplant recipients. It is likely that some of the decline in MMF use between discharge and 1 year post-transplant is due to its side effects (unspecified). Significant risk factors associated with higher 5-year mortality, conditional upon surviving the first post-transplant year, were female sex and history of treated rejection during the first post-transplant year.
	Rationale for Classification of Evidence: Large sample (>100), retrospective pediatric heart transplant report of the International Thoracic Organ Transplant Registry with a focus on infant transplant recipients, less than one year of age at the time of transplant.			

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
Conference abstract (limited information provided)				
Hingler et al. 2013	Prospective study to check EBV load in paediatric HTx patients in regard to their immunosuppressive therapy. Patients with CsA-Eve and CsA-MMF were compared in a sub analysis. Median time post-Tx was 7.5 years (range: 0.2-17.5). Comparator arm: Yes.	CsA+MMF (not known). CsA+Eve (not known). Dosing and formulation of MMF and CsA not reported.	N=39; unknwon number of patients received MMF. Median age: 13.8 years (2.9-26.5). Gender not specified.	Patients on CsA+MMF showed a reduced EBV-activity compared to patients on CsA+Eve. Compared to CsA+Eve, CsA+MMF seems to improve EBV-specific CD8+ T-cells response in paediatric HTx recipients with same exposure of CsA.
	Rationale for Classification of Evidence: This is a prospective small-sample (<50) study to assess the impact of immunosuppressive therapy on anti-EBV specific CD8+ T-cells in pediatric heart transplant recipients providing comparison between CsA+MMF and CsA+ Everolimus treatment regimen.			
Kis et al. 2016	To summarise the complications after paediatric HTx since 2007. Regular controls were timed every 2-6 weeks, mean follow up was 3.4 (2.1) years. Comparator arm: No	Initial immunosuppressive therapy was TAC and MMF. Dose and formulation not reported.	N=29; number of paediatric patients on MMF unknown. Age: 7.1 years old. Gender not specified.	Six of the 29 patients experienced MMF related gastrointestinal problems for which MMF was withdrawn and Eve was given.
	Rationale for Classification of Evidence: This is a retrospective small-sample (<50) single-centre study with a primary objective to summarise complications after pediatric heart transplantation.			
Lehmkuhl et al. 2011	Clinical study to evaluate safety and efficacy of Eve in comparison to MMF during follow-up of 24 months. Comparator arm: Yes	Group A: Eve; n=24. Group B: MMF; n=28 (dose and formulation not reported). All patients received CsA as de-novo immunosuppressive and were followed-up for 24 months.	N=52; 28 received MMF. Age <18 years. Gender not specified.	4 patients (16.1%) in Group A, and 5 patients (17.8%) in Group B developed CAV at 12 months. CMV infection occurred in 1 patient (4%) in Group A, and 4 patients (14.2 %) in Group B. Six children died (n=1 in Group A, and n=5 in Group B). Two children died due to acute cellular rejection (Group B). Side effects such as infections, hospitalisation rates, haemoglobin concentration, platelet count, the development of lymphoproliferative disease and cholesterol values were similar between the groups.
	Rationale for Classification of Evidence: This small-sample (<50) study evaluates efficacy, safety and survival during follow-up of 24 months for Eve in comparison to MMF.			

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
Nunoda et al. 2013	Prospective observational study of HTx patients before the age of 18 years. Median time post-Tx was 7.5 years (range: 0.2-17.5). Comparator arm: No	All patients received standard triple therapy including CsA or TAC, MMF (dose and formulation not reported), and a corticosteroid.	N=26; all received MMF. Age: 7.6±4.2 years. Males:females=16:10.	Patient survival at 1, 5, 10, and 20-years post-Tx was 96.2%, 91.3%, 85.3%, and 85.3%, respectively. Paediatric survival rates were better than adult survival rates that were 94.7% at 1 year, 94.7% at 5 years, 81.2% at 10 years, and 72.2% at 15 years. One patient died of CAV at 4.8 years after HTx and one due to PTLD at 7.3 years after HTx Adverse events during the late post-Tx period included CAV (n=3), PTLD (n=4), and renal dysfunction (n=2), however time to onset of these events after initiation of MMF was unknown.
	Rationale for Classification of Evidence: This is a single-centre retrospective review providing long term follow up data on a small sample of patients on MMF containing regimens (<50).			
Reichel et al. 2000	Retrospective comparative assessment of paediatric patients receiving HTx during 82 patient-month of immunosuppression with MMF and a historical group of paediatric patients who received HTx during 41 patient-month treatment with AZA. Duration of the study was not specified. Comparator arm: Yes	MMF (N = 8). AZA (N = 6). Dosing and formulation of MMF and AZA not reported.	N = 14; 8 received MMF. Age range: 6 months to 9 years (mean age: 3.5 years). Gender not specified	Frequencies of infection during immunosuppression were 0.21 per patient-month during treatment with MMF, and 0.44 per patient-month during treatment with AZA, and frequencies of severe infections were 0.17 per patient-month for MMF and 0.10 per patient-month for AZA. Frequencies of rejection episodes were zero for MMF and 0.17 per patient- month for AZA.
	Rationale for Classification of Evidence: Small sample (<50) retrospective comparative assessment of paediatric HTx patients on MMF to paediatric HTx patients on AZA.			

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
Consensus statement				
Singh et al. 2016	Consensus statement.	Initial dosing for MMF is recommended at 600 mg/m^2/dose b.i.d to a maximum of 2,000 mg/day. Formulation of MMF not reported.	Not specified.	MMF has replaced AZA in most centres as it appears to be more specific for lymphocytes than AZA, and fewer adverse events are exhibited with its use. Adverse events are largely dose related and include leukopenia, anaemia, nausea, vomiting, and diarrhoea.
	Rationale for Classification of Evidence: Consesus statement reporting the trends in immunosuppression for paediatric heart transplant recipients.			

AZA = azathioprine; b.i.d. = twice a day; CAV = cardiac allograft vasculopathy; CI = confidence interval; CMV = cytomegalovirus; CNI = calcineurin inhibitor; CsA = ciclosporin A; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; Eve = everolimus; HTx = heart transplant(ation); IV = intravenous; MMF = mycophenolate mofetil; MPA = mycophenolic acid; MPS = mycophenolate sodium; OR = odds ratio; PCR = polymerase chain reaction; PTLD = post-transplant lymphoproliferative disorder; RTMCE = real-time myocardial contrast echocardiography; SmPC = Summary of product characteristics; Tx = transplant(ation); TAC = tacrolimus; WBC = white blood cell.

Table 34 Summary of Paediatric Liver Transplant Studies Contributing to Safety Evaluation

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
Prospective				
Dehghani et al. 2010	Prospective analysis of neuromuscular complications in 48 paediatric patients with LTx. Mean duration of follow-up was 21.6±9.4 months. Comparator arm: No	Immunosuppressive medication consisted of TAC (n=44) or CsA (n=4) combined with MMF (n=33), and prednisolone (n=18). Dosage and formulation of MMF not reported.	N=48; 33 received MMF. Mean age: 9.6±4.3 years. Males:females=30:18.	Of the 48 patients receiving immunosuppression by MMF, prednisone, TAC and CsA, 20 developed neurologic complications of which 17 were on MMF combination therapy. The most-common neurologic complications reported in all these patients were tremor (n=8, 16.7%), convulsions (n=6, 12.5%), insomnia (n=6, 12.5%), headache (n=5, 10.4%), muscle cramps (n=5, 10.4%), paraesthesia (n=3, 6.2%), and weakness (n=3, 6.2%). The authors concluded that most-common neurologic complication after LTx in children is tremor, same as in adult patients, which may be due to higher rate of use of TAC in these patients.
	Rationale for classification of evidence: This is a prospective, single-centre analysis focused on neuromuscular complications in a small sample (<50) of paediatric patients with LTx.			
Ferraris et al. 2004	Prospective analysis to study effect of MMF initiation and reduction in CsA dose in paediatric LTx with chronic renal dysfunction secondary to CsA toxicity. The total duration of reduced doses of CsA combined with MMF was 24 months. Comparator Arm: No	Reduced dose CsA (target trough level: 40–90 ng/ml) combined with 600 mg/m² b.i.d MMF for 24 months.	N=11; all received MMF. Mean age: 6.2±0.4 years at transplantation, and 12.5±2 years at start of the study. Males:females=5:6.	Reduction of CsA dose combined with initiation of MMF resulted in a significant improvement in renal function and reduction of microalbuminuria in paediatric LTx recipients with chronic renal dysfunction secondary to CsA nephrotoxicity. According to the Authors, MMF allows the safe reduction of CsA, with an improvement in renal function, no risk of rejection, and minor changes in the immune response.
	Rationale for Classification of Evidence: This is a single-centre small sample (<50) prospective study evaluating the potential for MMF to enable CNI reduction and recovery of renal function.			
Retrospective				
Aw et al. 2008	Retrospective study to evaluate the long-term outcome of MMF rescue therapy for steroid resistant rejection in paediatric liver allograft recipients The median time to MMF rescue therapy was 1.8 months (range: (0.4–35.8). The median follow-up was 8.8 (range: 7.7–11.5) years. Comparator arm: No	MMF (formulation not reported) started at 10 mg/kg/day in divided doses and increased to 4,010 mg/kg/day over two weeks in biopsy-proven cellular rejection that had failed to improve following at least one 3-day course of IV pulse steroid. Primary immunosuppression was CsA-based in 22, and TAC-based in 6 patients.	N=26; all received MMF. Age: 4.8 months–13.6 years (median: 1.7 years) Males:females=10:16.	12 subjects developed adverse events related to MMF: diarrhoea (n=5), vomiting (n=1), abdominal pain (n=1), protein losing enteropathy (elevated stool alpha-1-antitrypsin levels; n=1), leukopenia (n=5), EBV seropositive (n=5, of which 3 developed PTLD). One subject stopped MMF temporarily because of neutropenia. Two subjects died: one due to graft dysfunction after the third Tx, and second due to PTLD (B cell lymphoma). Six children had GFR <80 mL/minute/ 1.73 m², 5 of whom had previously stopped MMF because of side effects. MMF was reintroduced in combination with a lower TAC dose in 4 children, with subsequent improvements in GFR in 3. Nephrotoxicity is a known adverse drug reaction of TAC. MMF was stopped in 6 children while it was restarted successfully in the remaining children.
	Rationale for Classification of Evidence: This is a retrospective single-arm study evaluating the use of MMF in rescue of steroid resistant rejection in a small group of patients (<50).			
Chardot et al 2001	Retrospective study to analyse the use of MMF as a rescue therapy in paediatric patients with LTx and to assess its efficacy and safety. Median follow-up after initiation of MMF therapy was 642 days (range: 229–1606). Comparator arm: No	Median initial dose of MMF was 23 mg/kg/day (range 12–43) orally. The median time interval between LT and initiation of MMF therapy was 130 days (range: 13–3732 days)	N=19; all received MMF. Age: 30 months (range: 7–149). Males:females=8:11.	Six patients (32%) experienced eight side effects, mainly gastrointestinal and haematological, which resolved after cessation of MMF in five cases and dose reduction in three. One case of PTLD occurred under MMF therapy (5.2%). Four patients had EBV primary infection, while under MMF therapy, without subsequent PTLD. Three patients had CMV primary infection, and five CMV reactivation, under MMF therapy. Seven remained asymptomatic, and one presented with CMV enteritis. One patient, with cardiomyopathy prior to LTx, died 18 months after a re-Tx, due to progression of the heart disease, whereas MMF therapy was stopped five months earlier. No patient died and no graft was lost, while under MMF therapy. Authors concluded that MMF is an effective and safe immunosuppressant in paediatric LTx recipients. Its use is hampered by frequent gastrointestinal and haematological side effects. MMF does not seem to increase the risk of PTLD nor CMV disease.
	Rationale for Classification of Evidence: This is a single-centre small sample (<50) retrospective analysis on the use of MMF as rescue in children with insufficient immunosuppression or allograft rejection.			

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
Colombani et al 2000	Retrospective study to review the complications of LTx surgery, immunosuppression, rejection, and overall survival rate in orthotopic LTx between November 1992 and October 1998. (5 years, 11 months). Comparator Arm: No	All but 4 recipients received primary TAC immunosuppressive regimens. The other 4 underwent conversion from CsA. Concomitant immunosuppression included steroid and MMF. MMF dose 600mg/m^2/12 hours (formulation not reported).	N=30; all 30 received MMF. Age:3 months to 7 years (mean age: 28 months). Gender not specified.	Complications of immunosuppressive therapy included persistent systemic hypertension (n=6), renal tubular acidosis (n=3), short-term hyperglycemia (n=2), neurotoxicity (n=2), nephrotoxicity (n=2), food allergies (n=8), PTLD (n=4). Two patients (n=2) required re-Tx. Post-operative surgical complications resulted in 4 early deaths (13%): 1 from primary nonfunction, 2 from sepsis, and 1 from renal failure-arrhythmia and cardiac arrest. There was one late death from recurrent disease from hepatitis. No information was available regarding the immunosuppressive drug that caused the complications of immunosuppressive therapy.
	Rationale for Classification of Evidence: This is a small-sample (<50) retrospective chart review to study complications of transplant surgery, immunosuppression, rejection, and overall survival rate in paediatric patients who received living-related liver transplantation.			
Evans et al. 2005	Retrospective study to evaluate effect of MMF in on renal function after MMF was started due to renal dysfunction in children with orthotopic LTx. The duration of observation was for at least 1 year. Comparator Arm: No	MMF monotherapy=36 (dose of 20 mg/kg per day in two divided doses; formulation not reported). MMF with low-dose CsA or TAC=8. MMF with steroids=4.	N=48; all 48 received MMF. Age: 10.8 months–18.1 years (median: 11.1 years). Males:females=23: 25.	In 44 (92%) patients, there was a statistically significant increase of cGFR, greater in children aged <3 years at Tx or who were <5 years post-Tx when MMF was started. Eight out of total 48 patients developed adverse events: transient bone marrow suppression with decreased WBC count in 3 patients, nausea and headache in 1 patient, alopecia mild and transient in 2 patients, gastrointestinal bleeding requiring discontinuation of MMF in 1 patient. Liver function abnormalities occurred in seven patients (15%): transient transaminitis in three, acute rejection in two, and chronic rejection in two, of whom one required re-Tx.
	Rationale for Classification of Evidence: A single-centre small sample (<50) retrospective analysis evaluating the potential for MMF to enable CNI reduction and recovery of renal function.			

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
Gavalda et al. 2012	This retrospective study included 49 paediatric solid organ transplant recipients (32 liver, 14 kidney, and 3 combined liver–kidney) paediatric patient (<18 years) who underwent liver, kidney, or liver–kidney transplantation and had microbiologically confirmed pH1N1 infection in 6 months study period in a single centre. Comparator Arm: No	Triple maintenance immunosuppressive regimens (TAC, CsA, 6-methylprednisolone, MMF and Eve). Dose, duration and formulation not reported.	N=49; 25 received MMF. Median age: 10 years (age range: 7–14 years).	All 49 patients developed confirmed pH1N1 of which pneumonia was diagnosed in 4 patients (8.2%), and 3 of them required respiratory support. However, the number of paediatric patients with LTx who were given MMF and further progressed to these adverse events is unclear. There were no related deaths.
	Rationale for Classification of Evidence: This is a small sample size (<50) retrospective study with a primary focus on H1N1/2009 infection in paediatric solid organ transplant recipients.			
Haflidadottir et al. 2022	Retrospective data collection from medical records, including total and specific immunoglobulin E (IgE), eosinophil cationic protein, and eosinophil count (12 months after transplantation and at yearly follow-up) to identify risk factors for development of food allergies in liver transplant children. Trough levels of MMF, and tacrolimus 3, 6, and 12 months after transplantation were recorded.	Dose and formulation not reported. Duration of MMF therapy varied from 0.2 months to more than 2 years. Median follow-up time was 7.6 years (2.5–13.6 years).	N=107; 85 on MMF Age at Tx= 1.9 years (8.4 months–8.3 years) Male:female=54:53	Altogether 85 patients were treated with MMF after transplantation, and 7 of those patients received MMF temporarily before MMF was part of the protocol. MMF had to be discontinued in 24 out of 78 patients (31%) due to side effects, such as neutropenia (n = 20), gastrointestinal symptoms (n = 3), and herpetic stomatitis (n = 1). Age at discontinuation of MMF was 1.5 (0.9– 8.6) years, and the time from transplantation to discontinuation of MMF was 0.4 (0.2–0.5) years. Only 7 out of 24 patients with food allergy had been treated with MMF 1 year after transplantation. Food allergy was less frequent in the children who received MMF in combination with tacrolimus 1 year after transplantation compared to patients not receiving MMF (12.5% vs 37.8%, P = 0.003). The patients treated with MMF at 1 year after transplantation also had less food sensitisation 1 year after transplantation (8.9% vs 17.8%, P = 0.02) and at any time (26.8% vs 57.8%, P = 0.002) compared to those not receiving MMF.
	Rationale for Classification of Evidence: This is a medium sample size retrospective data analysis of medical records with a primary focus on risk factors for development of food allergies in liver transplant children.			

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
Honda et al. 2018	To analyse the long-term outcomes of paediatric patients who underwent ABO-i living donor LTx and to assess the adequacy of the immunosuppressive protocol against the ABO-barrier between December 1998 and March 2016 (17 years, 3 months). Comparator arm: Yes	MMF given 10 mg/kg b.i.d, orally. Group 1: ABO-i n=29 TAC+ Steroid+ MMF In adjunction, paediatric LDLT (2 ≤ age < 18; n = 10) received additional rituximab. Group 2: Non-ABO-i n=131 TAC plus steroid.	N=160; 29 received MMF. Group 1: n=29 patients (10 male, mean age: 3 year) Group 2: n=131 patients (58 male, mean age: 4.6 years).	For 29 patients on MMF in Group 1: 10 (34.5%) developed bacterial infection, 14 (48.3%) developed CMV infection, 13 (44.8%) developed acute cellular rejection, 3 (10.3%) developed biliary complications, 3 developed portal vein stenosis/portal vein thrombosis (10.3%), 2 (6.9%) developed antibody-mediated rejection, and fungal infection, hepatic vein stenosis and hepatic artery stenosis were reported in 3 single patients (3.4% each). During the study period, mortality rate in non–rituximab treated ABOi group was 15.8%, and in rituximab-treated ABOi group was 30.0%. The cause of death in the former group was heart failure (in related to the primary disease, glycogen storage disease type IV), pulmonary hypertension (in related to the primary disease, mitochondrial DNA depletion syndrome), and interstitial pneumonia. The cause of death in the latter group was AMR in 2 patients and the other was multiple organ failure related to complications of the primary disease (progressive familial intrahepatic cholestasis type 1) including bleeding from the ileostomy, severe.
	Rationale for Classification of Evidence: This is a small sample size retrospective data analysis of long-term outcomes of paediatric patients who underwent ABO-i living donor LTx and of adequacy of the immunosuppressive protocol against the ABO-barrier.			
Imanieh et al. 2022	This study aimed to determine the prevalence of post-transplant lymphoproliferative disorder (PTLD) based on the clinical and epidemiological characteristics of donors and pediatric transplant recipients aged <18	MMF dose was unclearly stated as a mean value from an unspecified number of patients on MMF. The immunosuppressive drugs (prednisolone, tacrolimus, silorimus, CellCept) were used for 14.79 ± 14.40 months from the time of transplantation until the date of PTLD diagnosis.	N=1207 (unknown how many on MMF) Age at LTx: PTLD group: 4.93 ± 1.07 years Non-PTLD group: 7.80 ± 5.54 Female:male ratio = 51.49% in the PTLD group and 44.56% in the non-PTLD group	The cumulative survival proportion was higher in males as well as in the patients aged under six years compared to females and the patients over six years old. Of 1207 patients (unknown how many on MMF), 49 were diagnosed with PTLD (4% prevalence).
	Rationale for Classification of Evidence: This is a retrospective study focused on post-transplant lymphoproliferative disorder in paediatric LTx.			

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
Leiskau et al. 2018	Patients after LTx receiving immunosuppression with MMF+TAC were compared to retrospectively selected age- and diagnosis-matched patients with TAC monotherapy and CsA+steroid therapy. Effectiveness, renal function and side effects were analysed for 1 year after LTx. Comparator arm: Yes	Group 1: MMF+TAC ; n=19 (MMF started 7 days post LTx; 10 mg/kg in 2 doses for 2 weeks gradually increasing to a maximum of 20 mg/kg/day (max. 2 × 750 mg) in 2 doses); formulation not reported. Group 2: TAC monotherapy; n=19. Group 3: CsA+steroid; n=19.	N=57; 19 received MMF. Age<18 years. Gender not specified.	Two patients in group 1 discontinued MMF treatment for 2 and 3 weeks, respectively, due to gastrointestinal adverse events but could restart with a reduced dose of 10 mg/kg/day. Leukopenia occurred in 3 patients during comedication with ganciclovir, but improved after discontinuation of ganciclovir. The patients in MMF+TAC showed a significantly higher risk of septicaemic bacterial or mycotic infections (68.4%) however exact number of patients who experienced these adverse events is unknown) compared to TAC (31.6%), but not the CsA group (57.6%). EBV reactivation occurred more frequently in CsA patients (84.2%) than in MMF/TAC (47.4) and TAC patients (52.6%) the same was true for other viral infections: 47.4% (CsA) *vs.* 15.8% (TAC).
	Rationale for Classification of Evidence: This is a small sample single-centre comparison of MMF containing regimen with a historic CNI comparator arm.			
Nayagam et al. 2022	Single-centre, retrospective, observational study to evaluate EBV status and EBV-related complications in paediatric autoimmune liver disease (AILD)	In LTx patients MMF (median duration) was 6 years [IQR,4.0-12.9], dose 24.3 mg/kg/day [IQR,16.4-33.1]).	N=245 (AILD) of whom 150 (61.2%) were females and 69 were on MMF. Median age at MMF start = 13.7 years LTx n=39; 19 of them on MMF. Male:female=14:25 , MMF use status unknown	Post-LTx EBV viraemia developed in 14 of 19 LTx recipients on MMF (73.7%), median time to viraemia was 53 days (IQR, 20-53). There was no association between pre-transplant MMF (P > 0.99) on development of EBV viraemia post-LTx or characteristics of post-LTx viraemia. No PTLD was identified in the MMF group, compared to two PTLD patients on AZA.
	Rationale for Classification of Evidence: A single-centre observational study focused on EBV status and complications in paediatric AILD patients with a small subpopulation of AILD liver transplant recipients on MMF.			
Öztürk et al. 2019	Retrospective study to determine potential adverse effects of immunosuppressive protocols after LTx in children between February 2006 and January 2018 (11 years, 11 months). Comparator Arm: No	Corticosteroid, TAC, and MMF were the primary immunosuppressive agents. MMF was started preoperatively at 20 mg/kg/day; formulation not reported and was continued for 1 year	N=60; all received MMF. Age: 6.1 years (range: 3 months to 17 years) Males:females=34: 26.	Diarrhoea was the adverse event reported as associated with MMF (number of cases unknown). In addition, 9 out of 60 patients had unusual adverse events, including 3 patients with haemolysis while on MMF and TAC. A positive dechallenge reported with TAC only with corrective treatment. Two patients had eosinophilic gastroenteritis, one of which treated with TAC alone, and the other with TAC and MMF; the event resolved in both cases after corrective treatment and drug withdrawal of TAC.

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
	Rationale for Classification of Evidence: Medium-size (50-100) retrospective study to determine potential adverse effects of immunosuppressive protocols after LTx in children.			
Renz et al. 1999	Retrospective study to compare post-Tx renal function, incidence of leukopenia, and drug tolerance in MMF, microemulsion-CsA, and steroid group (CNp group), with AZA, oil-based gel-encapsulated CsA, and steroid with anti-T cell antibody induction therapy group (ACp group). Follow-up median (range, months) are CNp: 21 (12-28) and ACp: 41(29-50). Comparator arm: Yes	CNp group: n=26. ACp group: n=19. MMF dose: initially at 10 to 12.5 mg/kg/dose (orally b.i.d.), with adjustments to avert gastrointestinal symptoms and leukopenia	N=45; 26 received MMF. Age: 1 month to 16 years (mean: 58 months; median: 31 months). Males:females=17:9.	No significant difference was observed between the two groups in serum creatinine level or incidence of leukopenia requiring medical therapy during the first year post-Tx. Gastrointestinal symptoms observed in CNp paediatric LTx recipients included nausea, vomiting, and diarrhoea, with an overall incidence of approximately 30%. Management of clinical symptoms by simple MMF dose reduction was routinely achieved along with the administration of oral gastric proton pump inhibitors. Only 1 patient (4%) converted to TAC-based immunotherapy secondary to gastrointestinal intolerance of CNp.
	Rationale for Classification of Evidence: This is a retrospective, small size (<50) single-centre study to describe the application of an immunosuppressive protocol using MMF, CsA, and prednisone as primary immunosuppression.			
Seo et al. 2020	Retrospective study to evaluate paediatric LTx recipients for EBV load in relation to diagnosis PTLD at least 6 months of follow-up). Comparator arm: No	Immunosupressive therapy with TAC, steroids and MMF was given. Dosage, formulation and duration of treatment not reported.	N=142; number of paediatric patients on MMF unknown. Median age: 1.5 years (range: 0.8–6.1). Males:females=68:74.	Of the total 142 patients (unknown how many on MMF) 100 developed EBV DNAemia; of whom 14/100 developed PTLD. Two patients (2/14, 14.3%) died at 38 months and 16 months after diagnosis with PTLD; the causes of death were hepatic failure and acute respiratory distress syndrome associated with Pneumocystis jiroveci pneumonia, respectively.
	Rationale for Classification of Evidence: This is a retrospective, single-centre study to monitor Epstein-Barr viral load for diagnosing posttransplant lymphoproliferative disorder in pediatric liver transplant recipients.			

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
Tannuri et al. 2007	Retrospective Study to evaluate renal function in patients who underwent orthotopic LTx between 1988 and 2003 (15 years). Comparator Arm: No	Renal function was evaluated by biochemical parameters in five phases: immediately prior to MMF administration; 3, 6, 12 and 24 months after the introduction of MMF. MMF 10 mg/kg (b.i.d.) and increased gradually to 40 mg/kg/day within a two-week interval; formulation not reported.	N=191; all received MMF. Age <18 years. Gender not specified.	82% showed improvement of renal function parameters in comparison with the pretreatment values prior to MMF.
	Rationale for Classification of Evidence: This is a single-centre, large sample size (>100) retrospective analysis evaluating the potential for MMF to enable CNI reduction and recovery of renal function.			
Vazin et al. 2022	Retrospective cohort study to examine the incidence, clinico-microbiological characteristics, risk factors, and treatment outcomes of bacterial infections in liver transplant pediatric patients under 18 years of following liver transplantation	Dosing and formulation not available. The mean time of infection after LTx was 7.87 ± 3.32 days.	N=80; 69 on MMF Age 6.0 ± 4.0 years (median 5.0 years) Male:female=52:28	Of the 69 patients on MMF 24 patients experienced bacterial infection. Multivariate regression analysis showed that the only risk factor for bacterial infections after LTx was the length of ICU stay. The mean time of infection after LT was 7.87 ± 3.32 days. Intra-abdominal surgical site infection (24.24%), co-infection (19.69%), urinary tract infection (19.69%), and bloodstream infection (19.69%) were the most common recorded infections. Unknown which adverse events were reported on MMF.
	Rationale for Classification of Evidence: This is a retrospective, medium sample (50-100) single-centre study to evaluate bacterial infections in liver transplant paediatric patients.			
Conference abstract (limited information provided)				
Balci Sezer et al. 2020	Retrospective study to evaluate infection as the major cause of morbidity and mortality after paediatric LTx who have received MMF as an immunosuppressant. Duration of study was not specified. Comparator arm: No	34 patients received standard immunosuppressive regimen after LTx consisting of TAC, MMF and steroids. Dose, formulation and duration not reported.	N=34; all received MMF. Age: 4–12 months (median: 8). Gender not specified.	27 out of 34 patients reported presence of at least one pathogenic organism within first six months of Tx. Klebsiella pneumonia was the most common isolated bacteria from bloodstream and abdominal catheters and urine cultures. Staphylococcus epidermidis was the most common isolated bacteria from subclavian catheter cultures. Only one recipient had CMV infection during this period. No information is provided regarding the frequency and severity of these events.
	Rationale for Classification of Evidence: This is a retrospective, small sample (<50) study with a primary focus on post-liver transplant infections.			

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
Hudert et al. 2019	Retrospective analysis to assess the clinical course of 10 paediatric patients after LTx who switched from a TAC based immunosuppression protocol to MMF monotherapy. Cumulative period of 480 patient treatment-months (median: 37.5 months, range: 11–103).	All patients received MMF (dose and formulation not reported).	N=10; all received MMF. Mean age: 14.5 years (range: 3–19). Gender not specified.	After switching to MMF, five biopsies in four patients were performed due to abnormal liver function tests, but no acute or chronic transplant rejection was noted. Diarrhoea associated with MMF occurred in one patient but ceased upon dose reduction. There were no persistent haematologic pathologies attributable to MMF.
	Rationale for Classification of Evidence: This is a retrospective, small sample (<50) study to assess the clinical course of liver transplant paediatric patients switched from TAC to MMF.			
Lightdale et al. 1997	Prospective, non-randomised study to analyse safety and effectiveness of MMF, CsA and steroid *vs.* AZA, CsA and steroid from December 1993 to October 1996 (2 years, 10 months). Comparator arm: Yes.	Group 1: MMF+CsA+steroid: n=20. MMF: 20-25 mg/kg b.i.d; formulation not reported. Group 2: AZA+CsA+steroid: n=20.	N=40; 20 received MMF. Median age: 17 months. Gender not specified.	9 patients (45%) in Group 1 (including MMF) and 13 patients (65%) in Group 2 (control group) experienced bone marrow suppression. There was no difference between Group 1 and Group 2 in change in serum creatinine at 6 months. At Year 1, Group 1 had a 100% survival rate *vs.* 95% in Group 2.
	Rationale for Classification of Evidence: This is a prospective, small sample (<50) study to compare the safety and effectiveness of two treatment regimens.			
Rauschenfels et al. 2009	In this prospective study, children after orthotopic LTx under therapy with MMF and CsA were compared with those under immunosuppression therapy with CNI. The median time was 4.7 (range: 1.1–15.6) years after orthotopic LTx, under a combined immunosuppressive therapy of MMF and CsA when compared with development of renal function in a historic control group with median time 5.1 (range: 1.0–10.7) years after orthotopic LTx	Group 1: MMF+CsA; n=25 Group 2: CNIs; n=51 (36 CsA, 15 TAC) Dosage and formulation of MMF not reported.	N=76; 25 received MMF. Age: 2–16.5 years. Group 1: male:female=14:11. Group 2: male:female=28:23. Gender not specified.	The GFR increased from 60 mL/min to 77 mL/min at 24 months in Group 1, and the GFR showed a decrease of 11% from 67±23 mL/min to 59±22 mL/min at 24 months in Group 2. MMF dosage had to be reduced due to gastrointestinal side effects in 2 patients. In 1 patient in Group 1 acute rejection occurred after refusal of medication, whereas in Group 2 no rejection was reported. Liver function tests and full blood cell counts in both groups showed no significant changes Introduction of MMF combined with reduced CsA dosage leads to better improvement of renal function of liver-transplanted recipients than group 2. Side effects under a close MMF monitoring were rare.

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
	under immunosuppression therapy with CNI. Comparator arm: Yes			
	Rationale for Classification of Evidence: This is a prospective, small sample (<50) study to compare two treatment regimens.			
Sadiq et al. 2013	Evaluate incidence of MMF-induced diarrhoea in paediatric LTx patients & formulate uniform policy about timing of introduction of MMF & suitable dose. In this two-phase study, the first phase, records of children who had LTx in last 1 year were reviewed. All patients who had LTx in next 6 months were included in second phase. Compactor arm: Yes (Two phase study)	Phase 1: retrospective analysis with conventional dose of MMF. (n=36) (dose and formulation not reported) Phase 2: Prospective study where, based on group 1 results, MMF dose was reduced (n=17). However exact dose after reduction was not reported.	N=53, all 53 received MMF. Age and gender not specified.	Phase 1: 25 (70 %) patients developed diarrhoea. Out of these 22 patients, (85.7 %) had moderate to severe diarrhoea. Phase 2: 12 (75 %) patients developed diarrhoea but only 5 (41.6 %) patients had moderate to severe diarrhoea. No information was available regarding whether the dose of MMF was reduced in response to diarrhoea.
	Rationale for Classification of Evidence: Two-phase (a small sample size (<50) prospective and a small sample size (<50) retrospective study) with a focus of MMF-induced diarrhoea.			
Teisseyre et al. 2006	This study compared the efficacy and safety of steroid free immunosuppression based on TAC and MMF with TAC and steroids. Duration of study was not specified. Comparator arm: Yes	Group 1: TAC+MMF (dose and formulation not reported); n=19. Group 2: TAC+steroids; n=20.	N=39; 19 received MMF. Age <18 years. Gender not specified.	Group 1 showed fewer events of EBV DNA copies, CMV infection and acute hepatitis than group 2.
	Rationale for Classification of Evidence: This is a small sample size (<50) single-centre retrospective analysis to compare the efficacy and safety of steroid free immunosuppression based on TAC and MMF with TAC and steroids.			

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
Teisseyre et al. 2011	Prospective, comparator study to analyse two methods of TAC-based immunosuppression with or without MMF. Duration of study was not specified. Comparator Arm: Yes	Group A: TAC+MMF (dose and formulation not reported): n=22. Group B: TAC+ steroids: n=22. MMF was administered from 0–90th day, and then reduced and discontinued finally 4 months after LTx.	N=44; 22 received MMF. Age range: 5.8 weeks–18.1 years. Gender not specified.	Group A (including MMF) showed reduced need for anti-hypertensive treatment in the early post-Tx period and 1- and 2-year post-Tx. Lower incidences of EBV infection was observed in group A at 1, 2 and 3 years after LTx. More patients from group A showed normal liver histology 1 year post-LTx, and the difference was not significant.
	Rationale for Classification of Evidence: This is a small sample size (<50) single-centre retrospective analysis evaluating the potential for MMF to enable CNI reduction and recovery of renal function.			
Weiner et al. 2012	Retrospective chart review of paediatric LTx recipients for primary infection with EBV and PTLD. Duration of study was not specified. Comparator arm: No	Induction with daclizumab (anti- IL-2 receptor antibody), steroids and MMF (15 mg/kg, b.i.d) with delayed initiation of TAC and maintenance steroids (mostly 6 months) followed by TAC monotherapy. MMF formulation not reported.	N=187; all received MMF. Age: 1 month–20 years (the study includes young adults between 18 and 20 years). Gender not specified.	EBV occurred in 46 patients (25%) and PTLD occurred in 16 (8.7%) patients. There was no increased risk of graft rejection for gender, age at or indication for LTx, graft type, pre- LTx EBV and antiviral treatment.
	Rationale for Classification of Evidence: This is a large sample size (>100) retrospective chart review with a focus on primary infection with EBV and PTLD.			

Study/ Reference	Study Design	Dosing, Formulation, Duration (Where Available)	Demographics	Key Findings
Wierderkehr et al. 2012	Prospective study to observe the frequency of the diarrhoea in MMF-treated LTx paediatric recipients and to compare this with adults LTx recipients. LTx recipients with persistent afebrile diarrhoea were prospectively investigated for infections and intestinal morphology integrity of the gastrointestinal tract and the results were compared with adults LTx recipients. Duration of study was not specified. Comparator arm: Yes	All patients received MMF (dose and formulation not reported). Dosing and concomitant medications not specified.	N=89; all received MMF. Mean age: 45 months. Males:females=34: 55.	4 of 89 developed permanent diarrhoea associated with loss of weight and dose of MMF was reduced (unspecified). Symptoms appeared 6 months after LTx in ¾ patients. All four children had erosive colitis and one had an infection associated. Substitution of MMF had good results without increased risk for rejection
	Rationale for Classification of Evidence: A medium sample size (50-100) prospective study to observe the frequency of the diarrhoea in MMF-treated LTx paediatric recipients and to compare the results with adult patients.			

AZA = azathioprine; ABOi= blood group incompatible; b.i.d = twice a day; cGFR = corrected glomerular filtration rate; CMV = cytomegalovirus; CsA = ciclosporin A; DNA = deoxyribonucleic acid; GFR = glomerular filtration rate; EBV = Epstein-Barr virus; Eve = Everolimus; IV = intravenous; LTx = liver transplant(ation); MMF = mycophenolate mofetil; PTLD = post-transplant lymphoproliferative disorder; TAC = tacrolimus; Tx = transplant(ation); WBC = white blood cell.

Heart Transplant Recipients

One infant-focused study (Singh et al. 2022) was identified in specific populations (e.g., newborns, toddlers, teenagers, etc), in which also female sex was reported as a gender-specific risk factor associated with higher 5-year mortality, conditional upon surviving the first post-transplant year.

The AEs commonly reported in the literature from HTx paediatric patients treated with MMF are infections, gastrointestinal disorders, and blood dyscrasias.

PTLD (post-transplant lymphoproliferative disorder) was reported as SAE in 4 of the 17 publications concerning HTx paediatric patients. In general, the incidence of PTLD in paediatric patients is higher than that in adults due to the higher incidence of pre-transplant negative EBV-serostatus among children who receive an EBV-seropositive organ (Nijland et al. 2016). This is reflected in the Special Warnings and Precautions for Use part of the currently approved CellCept SmPC Section 4.4, which states "Patients receiving immunosuppressive regimens involving combinations of medicinal products, including mycophenolate mofetil CellCept, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.8). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent."

CAV (cardiac allograft vasculopathy) is another common serious complication occurring after HTx and is a major cause of graft loss and death. The frequency of occurrence increases, from approximately 30% of patients at 5 years after HTx, to 50% of patients at 10 years after HTx.

Liver Transplant Recipients

One study that aimed to determine the prevalence of PTLD (Imanieh et al. 2022) reported that the cumulative survival proportion was higher in males as well as in the patients aged under six years compared to females and the patients over six years old.

Based on the available literature, the AEs commonly reported in paediatric LTx patients treated with MMF were infections, gastrointestinal disorders and blood dyscrasias such as leukopenia and anaemia. These are all identified risks associated with MMF.

As for HTx, post-operative complications are a leading cause of mortality in paediatric LTx patients. Colombani et al (2000) reviewed the complications of transplant surgery, immunosuppression, rejection, and overall survival-rate in 30 paediatric patients aged 3 months to 7 years receiving orthotopic LTx between 1992 and 1998. All patients received MMF at a dose of 600 mg/m2 b.i.d. The authors reported 4 early deaths (13%), 1 from primary non-function, 2 from sepsis, and 1 from renal failure, arrhythmia and cardiac arrest.

Five of the 26 publications concerning paediatric LTx patients reported PTLD.

Analysis of Individual Case Safety Reports in the Roche Global Safety Database

An analysis of cumulative data from the international birth date of MMF (i.e., 3 May 1995) up to 31 December 2022 was conducted for AE reports concerning adult and paediatric patients with renal, liver or heart transplant. Limited aggregate data are available with respect to the extent of MMF exposure, including data on doses received, dose intensity, etc.

The resulting aggregate data were analysed in terms of proportion of AEs. The analysis aimed to compare the proportions of AEs reported in paediatric HTx or LTx patients with the proportions of AEs reported in adult HTx or LTx patients, respectively. For paediatric patients, the proportions of AEs reported in patients with HTx or LTx (i.e., off-label use) were also compared with the proportion of AEs reported in patients with RTx (i.e., on-label use).

The estimated cumulative patient exposure to MMF in Company-sponsored interventional clinical trials where MMF was used as an investigational drug in any investigated indication is 16,226 patients, of which 451 patients were < 18 years old. Of these, a certain number of patients have received MMF for already approved indications (e.g., RTx), or were exposed to MMF within an immunosuppressive protocol or as background therapy, so were not within the scope of this submission. The only study providing specific safety data relevant for inclusion in this submission was Study PA16497 (discussed above).

As of 2 May 2022, since the international birth date (3 May 1995), the estimated cumulative post-marketing patient exposure to MMF in any indication (i.e., both on-label and off-label) was 8.86 million patient-years. No specific data are available for post-marketing exposure to MMF in paediatric patients.

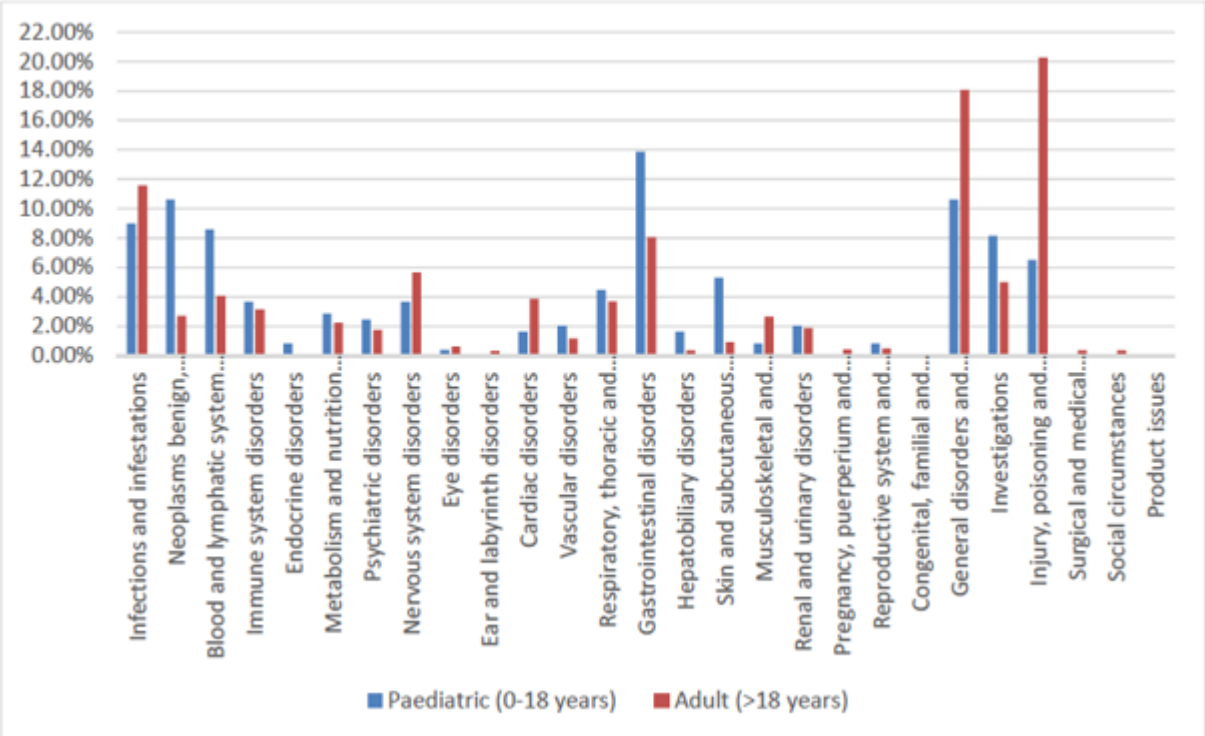
Table 35 Distribution of Individual Case Safety reports and Adverse Events Reported in Paediatric versus Non-Paediatric Age Group

Reports	Paediatric Age Group	Non-Paediatric Age Group
Renal Transplant		
ICSRs	464	10,359
AEs	1,477	21,596
Heart Transplant		
ICSRs	74	961
AEs	245	2,556
Liver Transplant		
ICSRs	114	2,267
AEs	287	4,825

AE = adverse event; ICSR = Individual Case Safety Report.

Paediatric versus Non-Paediatric HTx Patients

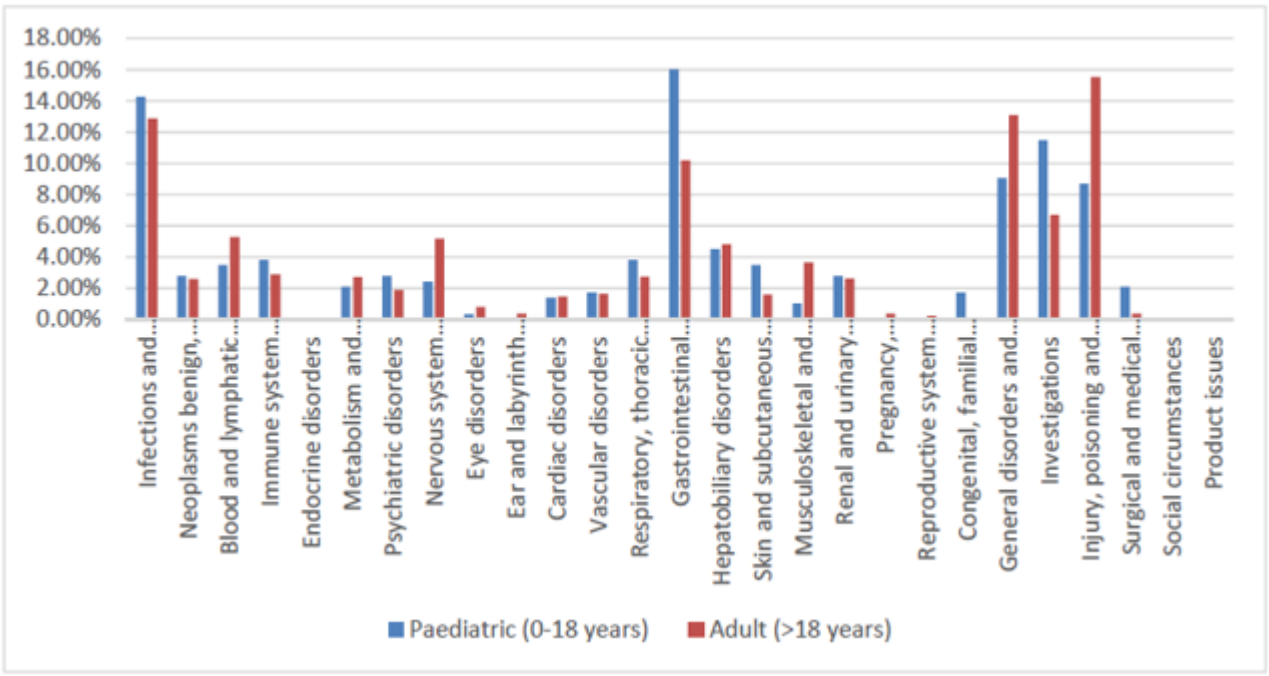
Figure 5 Proportion of All AEs by SOC in Paediatric versus Non-Paediatric Patients with Heart Transplant



An evaluation of the SAEs reported in paediatric versus non-paediatric HTx patients confirmed the imbalances for the SOCs Neoplasms Benign, Malignant and Unspecified (15.2% vs. 5.9%), Gastrointestinal Disorders (12.9% vs. 8.3%), and Blood and Lymphatic System Disorders (11.7% vs. 7.2%). Whereas the predominant SAEs were driven by well-described adverse drug reactions (ADRs) of MMF (e.g., PTLD and gastric ulcer), and the limitations of post-marketing reports preclude an accurate assessment of frequency, it is possible that even minor gastrointestinal events such as vomiting or diarrhoea may lead to greater seriousness and/or severity in infants and children, for example due to dehydration or other complications.

Paediatric versus Non-Paediatric LTx Patients

Figure 6 Proportion of All AEs by SOC in Paediatric versus Non-Paediatric Patients with Liver Transplant

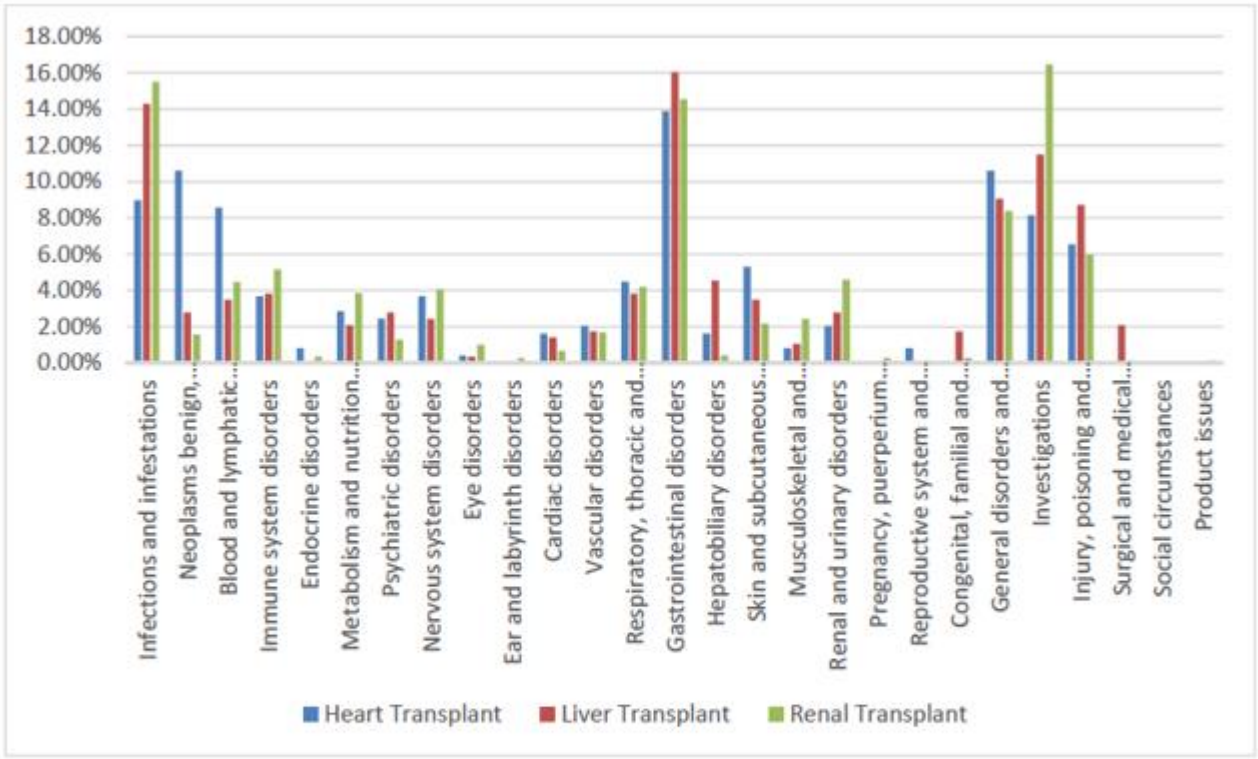


A markedly higher proportion (i.e., ≥ 3%) of AEs in paediatric patients was observed for the SOCs Gastrointestinal disorders (16.0% vs. 10.2%) and Investigations (11.5% vs. 6.7%). The imbalance under GI SOC was driven by adverse drug reactions such as diarrhoea, vomiting, and abdominal pain.

A markedly higher proportion (i.e., ≥ 3%) of SAEs in paediatric patients was mainly observed for the SOCs Gastrointestinal disorders (16.8% vs. 9.5%), and Surgical and medical procedures (3.5% vs. 0.5%). The vast majority of the SAEs reported in the SOCs Gastrointestinal disorders (e.g., diarrhoea, vomiting, duodenal ulcer, GI haemorrhages, pancreatitis) are adverse drug reactions associated with MMF and are described in the SmPC, which warns prescribers about these risks. Nevertheless, it is possible that even minor gastrointestinal events such as vomiting or diarrhoea may lead to greater seriousness and/or severity in infants and children, for example due to dehydration or other complications.

Paediatric HTx and LTx versus Paediatric RTx

Figure 7 Proportion of All AEs by SOC in Paediatric HTx and LTx Patients vs Paediatric RTx



AE = adverse event; HTx = heart transplant; LTx = liver transplant; SOC = system organ class; RTx = renal transplant.
x-axis indicates name of SOCs
y-axis indicates proportion of AEs (%)

For HTx, a higher proportion of AEs was reported for the SOCs Neoplasm Benign, Malignant and Unspecified (10.6% vs. 1.6% in paediatric RTx), Blood and Lymphatic System Disorders (8.6% vs. 4.5% in paediatric RTx), and Skin and Subcutaneous Tissue Disorders (5.3% vs. 2.2% in paediatric RTx). The imbalance observed between the AEs reported under these SOCs across paediatric patients receiving HTx versus RTx might be explained by the very small number of reports from HTx (n=74) and RTx (n=464) recipients. In the SOC Neoplasms Benign, Malignant and Unspecified an additional explanation might be related to the higher level of immunosuppression usually achieved in HTx patients. This is supported by Mynarek et al. (2013), who reported an incidence of PTLD between 1%–10% in RTx; 4%-15% in LTx, and 6%–20% in lung, heart, and heart-lung transplants. The nature and frequency of the reported SAEs from SOCs Neoplasm benign, malignant and unspecified, Blood and Lymphatic System Disorders and Skin and Subcutaneous Tissue Disorders did not raise new safety concerns.

In paediatric patients with LTx a higher proportion of AEs when compared to paediatric patients with RTx was mainly seen for the SOCs Hepatobiliary Disorders (4.5% vs. 0.4%) and Injury, Poisoning and Procedural Complications (8.7% vs. 6.0%). A review of the AEs reported under the SOC Hepatobiliary Disorders showed events expected in LTx patients, which constituted either post-operative complications of LTx with unlikely association to MMF or were the result of LTx rejection. Most of the reports received under SOC Injury, Poisoning and Procedural Complications represent medication errors which could be related to the lack of guidance provided to the prescriber for paediatric LTx, as this indication is off-label worldwide (with the recent exception of the US and Pakistan). The nature and frequency of the reported SAEs from SOC Hepatobiliary Disorders and SOC Injury, Poisoning and Procedural complications in LTx patients did not raise new safety concerns.

Studies performed in Renal Transplant Paediatric Patients

Study MYC2190 was an open-label, dose ranging, pharmacokinetic, safety and tolerance study of oral mycophenolate mofetil in the prevention of rejection in paediatric renal allograf recipients. 33 paediatric renal transplant patients were recruited, aged 3 years to 18 years, who were given 23 mg/kg of mycophenolate mofetil orally, twice daily. Overall, the safety profile in these 33 children and adolescents was similar to that observed in adult recipients of solid organ allografts.

Study MYCS2675 was an open-label, safety, tolerance, and pharmacokinetic study of oral mycophenolate mofetil suspension in the prophylaxis of rejection in paediatric renal allograft recipients. 100 paediatric renal transplant patients aged 1 to 18 years were recruited. The type and frequency of adverse reactions in patients who were given 600 mg/m2, up to 1 g/m2 of mycophenolate mofetil orally, twice daily, were comparable to those observed in adult patients given 1 g mycophenolate mofetil twice daily. A summary of the more frequently occurring adverse reactions is shown in **Table 36** below:

Table 36 Summary of adverse reactions observed more frequently in a trial investigating mycophenolate mofetil in 100 paediatric renal transplant patients (age/surface area-based dosing [600 mg/m^2, up to 1 g/m^2 BID.])

Adverse reaction **(MedDRA)** **System Organ Class**	**<6 years (n=33)**	**6-11 years (n=34)**	**12-18 years (n=33)**
Infections and infestations	Very common (48.5%)	Very common (44.1%)	Very common (51.5%)
Blood and lymphatic system disorders			
Leukopenia	Very common (30.3%)	Very common (29.4%)	Very common (12.1%)
Anaemia	Very common (51.5%)	Very common (32.4%)	Very common (27.3%)
Gastrointestinal disorders			
Diarrhoea	Very common (87.9%)	Very common (67.6%)	Very common (30.3%)
Vomitting	Very common (69.7%)	Very common (44.1%)	Very common (36.4%)

Based on limited sub-set data (i.e. 33 of the 100 patients) there was a higher frequency of severe diarrhoea (common, 9.1%), and candida mucocutaneous (very common, 21.2%) in children under 6 years of age, compared to the older paediatric cohort in which no cases of severe diarrhoea were reported (0.0%) and candida mucocutaneous was common (7.5%).

Renal Transplant Patients Less Than Two Years of Age

The CellCept dosage recommendations in the EU for the prophylaxis of acute transplant rejection in patients receiving allogeneic RTx currently exclude patients below 2 years of age. Of the 464 cases reporting 1,477 AEs for the paediatric age group receiving MMF for RTx, 12 cases containing 56 events concerned patients below 2 years who underwent kidney transplantation (cases of in utero exposure to MMF due to a maternal kidney transplantation were excluded). All patients were infants, of whom 11 patients were older than 3 months and in one case solely the age group infant was reported.

Nine of the patients were male, two of the patients were female and for one patient sex was unknown. Bearing in mind the limitations of the relatively small infant patient sample in the Roche Global Safety Database, this imbalance is in line with the higher proportion of male infants receiving RTx observed by Hogan et al. (2016). Using data from renal registries in 35 European countries, these authors reported 442 male versus 232 female transplant recipients of age less than one year and 207 male versus 128 female recipients of age from one to two years between 1 January 2000 and 31 December 2012.

For paediatric RTx, the highest proportion of AEs was reported for the SOC Investigations (16.5%), followed by Infections and infestations (15.5%), and Gastrointestinal Disorders (14.6%). The proportions of AEs for all remaining SOCs were below 10%.

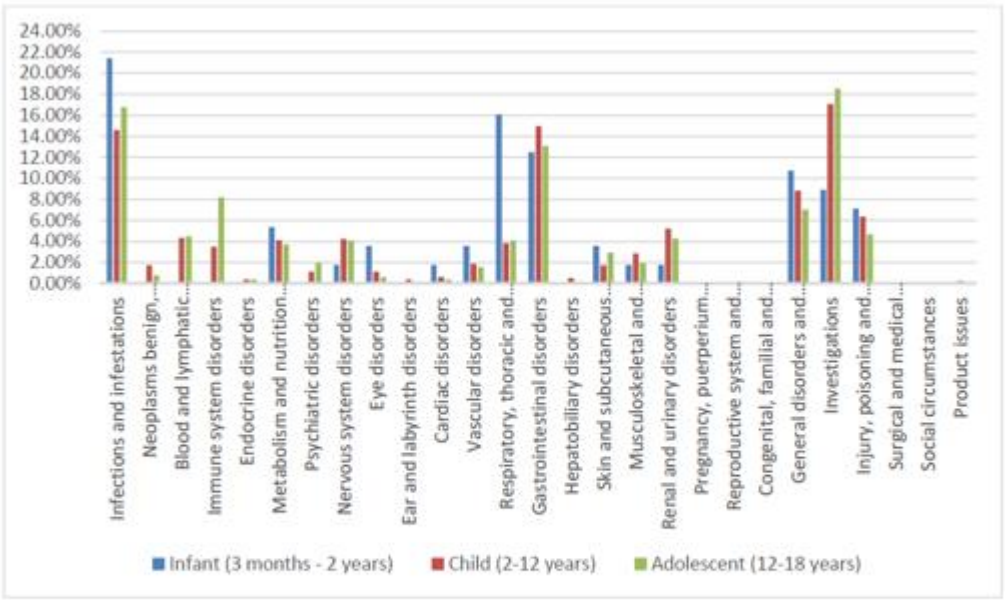
The proportions of all AEs by SOC in infant, child and adolescent RTx patients is presented in **Figure 8** and **Table 37**. A disproportion of ≥ 3% of reported AEs in infants compared to children and adolescents was noted in the SOCs Respiratory, Thoracic and Mediastinal Disorders (16.1% vs. 3.9% and 4.1%, respectively) and Infections and Infestations (21.4% vs. 14.6% and 16.8%, respectively).

An analysis of the AEs from SOC Respiratory, Thoracic and Mediastinal Disorders showed that the majority (5 AEs) were non-serious in nature. All 9 events under this SOC were reported in two patients which can explain the disbalance between the AE proportions in infant patients vs. patients from other age groups. Infections are in line with the safety profile of MMF and are due to its immunosuppressive properties.

The proportion of AEs in the SOC General Disorders and Administration Site Conditions was comparable for infants and children RTx recipients (10.7% vs. 8.9%) and were slightly higher in infants compared to adolescents (10.7% vs. 7.0%). The most reported AE from SOC General Disorders and Administrative Site Conditions both in the infant and child age group of RTx recipients was pyrexia (5.4% and 2.5%), while the proportion of pyrexia to all reported AEs in adolescent patients was 1.8%. In two of the three infant RTx patients for whom pyrexia was reported, an infectious condition was also present, insufficient information was provided for the third patient.

According to Jalanko et al. (2016), MMF use in this age group of patients was 60% and important long-term issues include infections, rejections, graft function, growth, bone health, metabolic problems, neurocognitive development, adherence to medication, pubertal maturation, and quality of life. Of those, only a relatively higher reporting rate for infections was observed in the Roche Global Safety Database in infants compared to other patient age groups.

Figure 8 Proportion of all AEs by SOC in Infants (3 Months to 2 years) vs Children (2-10 Years) and Adolescents (12-18 Years) with RTx



AE = adverse event; SOC = system organ class; RTx = renal transplant.
x-axis indicates name of SOCs
y-axis indicates proportion of AEs (%)

Table 37 Proportion of all AEs by SOC in Infants (3 Months to 2 years) vs Children (2-10 Years) and Adolescents (12-18 Years) with RTx

System Organ Class	Infant Renal Transplant (3 months to 2 years)		Child Renal Transplant (2-12 years)		Adolescent Renal Transplant (12-18 years)	
	Event Count	Proportion %	Event Count	Proportion %	Event Count	Proportion %
Infections and Infestations	12	21.43%	117	14.59%	86	16.76%
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	0	0.00%	14	1.75%	4	0.78%
Blood and Lymphatic System Disorders	0	0.00%	35	4.36%	23	4.48%
Immune System Disorders	0	0.00%	28	3.49%	42	8.19%
Endocrine Disorders	0	0.00%	3	0.37%	2	0.39%
Metabolism and Nutrition Disorders	3	5.36	33	4.11%	19	3.70%
Psychiatric Disorders	0	0.00%	9	1.12%	10	1.95%
Nervous System Disorders	1	1.79%	34	4.24%	21	4.09%
Eye Disorders	2	3.57%	9	1.12%	3	0.58%
Ear and Labyrinth Disorders	0	0.00%	3	0.37%	1	0.19%
Cardiac Disorders	1	1.79%	5	0.62%	2	0.39%
Vascular Disorders	2	3.57%	15	1.87%	8	1.56%
Respiratory, Thoracic and Mediastinal Disorders	9	16.07%	31	3.87%	21	4.09%
Gastrointestinal Disorders	7	12.50%	120	14.96%	67	13.06%
Hepatobiliary Disorders	0	0.00%	4	0.50%	1	0.19%
Skin and Subcutaneous Tissue Disorders	2	3.57%	14	1.75%	15	2.92%
Musculoskeletal and Connective Tissue Disorders	1	1.79%	23	2.87%	10	1.95%
Renal and Urinary Disorders	1	1.79%	42	5.24%	22	4.29%
Pregnancy, Puerperium and Perinatal Conditions	0	0.00%	0	0.00%	0	0.00%
Reproductive System and Breast Disorders	0	0.00%	1	0.12%	1	0.19%
Congenital, Familial and Genetic Disorders	0	0.00%	0	0.00%	0	0.00%
General Disorders and Administration Site Conditions	6	10.71%	71	8.85%	36	7.02%
Investigations	5	8.93%	137	17.08%	95	18.52%
Injury, Poisoning and Procedural Complications	4	7.14%	51	6.36%	24	4.68%
Surgical and Medical Procedures	0	0.00%	1	0.12%	0	0.00%
Social Circumstances	0	0.00%	0	0.00%	0	0.00%
Product Issues	0	0.00%	2	0.25%	0	0.00%
Total	**56**	**100.00%**	802	**100.00%**	513	**100.00%**

Bearing in mind the relatively small number of infant patients in the Roche Global Safety Database (n=12), for some of whom multiple events were reported, all PTs reported in infant RTx patients are presented in **Table 38**. The PTs reported for more than one infant patient were diarrhoea, pyrexia (3 each; 5.4% of all reported AEs) cough and nasal congestion (2 each; 3.6%). Of the 23 SAEs reported under this SOC in infant kidney transplant patients, 4 events resolved, 4 were resolving at the time of reporting, one was not resolved, and one had a fatal outcome. The outcome was unknown for the remaining 13 SAEs. For the eight events reporting resolution, MMF dose was unchanged in two instances, MMF dose was reduced or discontinued in response to two events, and the status of MMF therapy was unknown in relation to four events.

Table 38 Overview of AEs Reported in Infant RTx Patients

SOC	PT	Nonserious	Serious	Total
Infections and Infestations	Bacteraemia	0	1	1
	Bronchiolitis	0	1	1
	Clostridium difficile colitis	0	1	1
	Cytomegalovirus viraemia	0	1	1
	Epstein-Barr viraemia	1	0	1
	Infection	0	2	2
	Peritonitis	0	1	1
	Polyomavirus-associated nephropathy	0	1	1
	Sepsis	0	1	1
	Viraemia	0	1	1
	Viral infection	1	0	1
Infections and Infestations Total		**2**	**10**	**12**
Metabolism and Nutrition Disorders	Dehydration	1	0	1
	Food intolerance	1	0	1
	Hypomagnesaemia	1	0	1
Metabolism and Nutrition Disorders Total		**3**	**0**	**3**
Nervous System Disorders	Cerebrovascular accident	0	1	1
Nervous System Disorders Total		**0**	**1**	**1**
Eye Disorders	Eye discharge	1	0	1
	Lacrimation increased	1	0	1
Eye Disorders Total		**2**	**0**	**2**
Cardiac Disorders	Acute myocardial infarction	0	1	1
Cardiac Disorders Total		**0**	**1**	**1**
Vascular Disorders	Arteriosclerosis	1	0	1
	Hypotension	1	0	1
Vascular Disorders Total		**2**	**0**	**2**
Respiratory, Thoracic and Mediastinal Disorders	Bronchial hyperreactivity	0	1	1
	Cough	1	1	2
	Dyspnoea	1	0	1
	Nasal congestion	2	0	2
	Respiratory disorder	0	1	1
	Rhinorrhoea	1	0	1
	Tonsillar hypertrophy	1	0	1

Respiratory, Thoracic and Mediastinal Disorders Total		**6**	**3**	**9**
Gastrointestinal Disorders	Abdominal pain	1	0	1
	Diarrhoea	3	0	3
	Obstruction gastric	0	1	1
	Retching	1	0	1
	Vomiting	1	0	1
Gastrointestinal Disorders Total		**6**	**1**	**7**
Skin and Subcutaneous Tissue Disorders	Dermatitis diaper	1	0	1
	Keloid scar	1	0	1
Skin and Subcutaneous Tissue Disorders Total		**2**	**0**	**2**
Musculoskeletal and Connective Tissue Disorders	Myalgia	1	0	1
Musculoskeletal and Connective Tissue Disorders Total		**1**	**0**	**1**
Renal and Urinary Disorders	Haematuria	1	0	1
Renal and Urinary Disorders Total		**1**	**0**	**1**
General Disorders and Administration Site Conditions	Feeling abnormal	1	0	1
	Influenza like illness	1	0	1
	Malaise	0	1	1
	Pyrexia	1	2	3
General Disorders and Administration Site Conditions Total		**3**	**3**	**6**
Investigations	Biopsy kidney abnormal	1	0	1
	Blood creatinine increased	1	0	1
	Blood immunoglobulin G decreased	1	0	1
	Blood potassium increased	1	0	1
	Blood urea increased	1	0	1
Investigations Total		**5**	**0**	**5**
Injury, Poisoning and Procedural Complications	Expired product administered	0	1	1
	Incorrect route of product administration	0	1	1
	Medication error	0	1	1
	Off label use	0	1	1
Injury, Poisoning and Procedural Complications		**0**	**4**	**4**
Total		**33**	**23**	**56**

The overall outcome of infant RTx has dramatically improved, with long-term patient and graft survivals of over 90 and 80 %, respectively. According to Jalanko et al. (2016), MMF use in infant RTx patients was 60% and important long-term issues include infections, rejections, graft function, growth, bone health, metabolic problems, neurocognitive development, adherence to medication, pubertal maturation, and quality of life.

Comparison of the reported adverse events by SOC and PT by transplant type compared to adult data.

The paediatric AEs included in the table below are only those reported in conjunction with the proposed dosing regimen of 600 mg/m^2 of MMF orally b.i.d. up to 900 mg/m^2 b.i.d. AEs reported in paediatric patients, in the absence of dosing information, or where the dosing regimen differs, have been excluded. Due to the variety of dosing regimens and study design in the literature articles, the frequencies of AEs for paediatric transplant patients are presented as reported in the original article with denominators ranging between 20 and 55 (for specific denominators refer to the **Table *39*** footer).

Table 39 Adverse Events Reported in Literature Articles - MMF Dose of 600 mg/m² up to 900 mg/m² b.i.d.

Preferred term (MedDRA) System Organ Class	**Paediatric heart transplant**	**Adult heart transplant[6]**	**Paediatric hepatic transplant**	**Adult hepatic transplant[6]**
	Frequency	Frequency	Frequency	Frequency
Infections and infestations				
Bacterial infections	No data	Very common	Common[4]	Very common
Viral infections	Very common[1,2]	Very common	Common[4]	Very common
Fungal infections	Common[1]	Very common	No data	Very common
Gastrointestinal disorders				
Abdominal discomfort	Very common[1]	No data	No data	No data
Abdominal pain	No data	Very common	Common[3]	Very common
Diarrhoea	Very common[1]	Very common	Very common[3]	Very common
Protein-losing gastroenteropathy	No data	No data	Common[3]	No data
Vomiting	No data	Very common	Common[3]	Very common
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Lymphoproliferative disorder	No data	Uncommon	Very common[3,4]	Uncommon
Blood and lymphatic system disorders				
Leukopenia	Very common[1]	Very common	Very common[3]	Very common
Myelosuppression	No data	No data	Very common[5]	No data
Neutropenia	No data	No data	Common[3]	No data
Immune system disorders				
Food allergies	No data	No data	Very common[4]	No data
Nervous system disorders				
Neurotoxicity	No data	No data	Common[4]	No data
Vascular disorders				
Hypertension	No data	Very common	Very common[4]	Very common
Metabolism disorders				
Hyperglycaemia	No data	Very common	Common[4]	Very common
Type 1 diabetes mellitus	Common[2]	No data	No data	No data
Glucose tolerance impaired	Common[2]	No data	No data	No data
Renal and tubular disorders				
Nephropathy toxic	No data	No data	Common[4]	No data
Renal failure	No data	No data	Common[4]	No data
Renal tubular acidosis	No data	No data	Very common[4]	No data
General disorders and administrative site conditions				
Death	Common[2]	No data	No data	No data
Multiple organ dysfunction syndrome	Common[2]	No data	No data	No data
Injury, poisoning and procedural complications				
Transplant dysfunction	No data	No data	Common[3, 4]	No data
Investigations				

Preferred term (MedDRA) System Organ Class	Paediatric heart transplant	Adult heart transplant[6]	Paediatric hepatic transplant	Adult hepatic transplant[6]
Cytomegalovirus test positive	Very common[2]	No data	No data	No data
Epstein-Barr virus antibody positive	No data	No data	Very common[3]	No data

b.i.d. = twice daily; MMF = mycophenolate mofetil; MedDRA = Medical Dictionary for Regulatory Activities.
Note: "No data" pertains to the recommended dosage based on the available publications.
[1]Dipchand et al. 2001 (21 patients, MMF dose 40±14 mg/kg)
[2]Singh et al. 2010 (55 patients, MMF dose 1200 mg/m^2)
[3]Aw et al. 2008 (26 patients, MMF dose 40 mg/kg)
[4]Colombani et al. 2000 (30 patients, MMF dose 600mg/m^2/every 12 hours)
[5]Lightdale et al. 1997 (20 patients on MMF, MMF dose 20-25 mg/kg b.i.d.)
[6]CellCept SmPC

Seriousness and severity were typically not provided except for fatal events. In paediatric HTx patients, Singh et al. (2010) reported 6 deaths (9.6%), 5 of which were early hospital deaths in the post-transplantation period due to multiple-organ failure.

In paediatric LTx patients, Aw et al. (2008) reported two deaths: one (3.8%) due to graft dysfunction after the third transplantation, and second (3.8%) due to post-transplant lymphoproliferative disorder (B cell lymphoma). Colombani et al (2000) reported that post-operative surgical complications resulted in 4 early deaths (13%): one (3.3%) from primary nonfunction, two (6.7%) from sepsis, and one (3.3%) from renal failure-arrhythmia and cardiac arrest. Additionally, there was one (3.3%) late death from recurrent disease from hepatitis.

Additional Safety Considerations

Although no pregnancy report concerning HTx or LTx patient was identified in the literature and cumulative safety reports, teratogenicity remains an important identified risk of MMF (Sifontis et al. 2006; Hoeltzenbein et al. 2012), and thus the relevant Warnings and Precautions in CellCept SmPC apply also to adolescents of child-bearing age.

Two reports of overdose in paediatric patients with HTx or LTx were identified in the cumulative safety dataset: the first occurred in a 13-year-old male patient with LTx, who on an unspecified date experienced overdose with no associated AEs (AER 611496). The second concerned a 9-month-old male patient with HTx who was accidentally administered a dose 10 times higher than prescribed, and developed abdominal distension, general physical health deterioration, intestinal ischaemia, metabolic acidosis, lactic acidosis, acute gastritis with haemorrhage, intestinal necrosis, and hyperglycaemia. Therapy with MMF was withdrawn and five days later the patient died due to these events. It is unknown whether an autopsy was performed (AER 2351337).

No literature is available on long-term follow up in paediatric HTx and LTx patients with MMF.

2.5.1. Discussion on clinical safety

No company-sponsored pivotal clinical trials were conducted to support the safety of MMF in the prophylaxis of organ rejection in paediatric recipients of allogeneic heart or liver transplants.

The presented clinical safety evidence to support the use of MMF in paediatric patients with HTx or LTx comes from:

- A literature review of published studies

- Post-marketing reports from the Roche Global Safety Database
- A discontinued clinical trial in paediatric patients with LTx

9 paediatric patients (between the ages of 9 months and 5 years) were enrolled and followed for 14 days in a dose finding Phase IV study (Study PA16497) evaluating the safety, tolerability and pharmacokinetics of oral MMF in paediatric liver transplant (LTx) recipients on concomitant treatment with ciclosporin A (CsA) and corticosteroids. The patients were treated with MMF doses per center practice (MMF doses of 200 - 424 mg/m2). The study was discontinued due to recruitment issues. One AE, pyrexia, was reported, which was mild in intensity and assessed by the investigator as unrelated to trial treatment. No other AEs were reported during the study. This study was considered only supportive. Due to limited safety evaluation in the study no safety conclusion could be reached.

Initially, the MAH did not provide an integrated summary of available clinical evidence which allows evaluation of efficacy and related safety of the specific dosing scheme of MMF proposed for use in paediatric HTx and LTx patients. Given the unknown safety profile at recommended doses (starting dose of 600 mg/m2 of mycophenolate mofetil orally twice daily and maintenance dose of 900 mg/m2 twice daily), a literature summary was considered supportive of the extrapolation from adults and other indications (RTx).

The MAH has, upon CHMP request, presented tabulated reported adverse events by SOC and PT by % and by transplant type (LTx and HTx) along with a comparison to the adult data for the recommended doses (starting dose of 600 mg/m2 of mycophenolate mofetil orally twice daily and increased dose of 900 mg/m2 twice daily).

The MAH also provided a comparison of safety database analysis for paediatric patients receiving MMF for unlabelled indication of HTx and LTx vs. for labelled indication of RTx. This analysis did not consider exposure dose or duration, regardless, the comparisons from the safety database are considered supportive of the extrapolation from adults and other indications (RTx).

Based on the review of the available published studies and post-marketing reports the type and frequency of the reported adverse reactions in hepatic and cardiac transplant patients were consistent with those observed in paediatric and adult patients following renal transplant.

However, neoplasms Benign, Malignant and Unspecified, Gastrointestinal Disorders, and Blood and Lymphatic System Disorders were observed more frequently in paediatric HTx and LTx patients in comparison to adult groups. Differences in adverse events were also observed between paediatric HTx and LTx patients in comparison to paediatric RTx group. Reasons for paediatric population being more prone to these events and differences between RTx-HTx-LTx indications, or possible longer term exposure in paediatric population have been discussed but causal relationship with cellcept cannot be excluded. Therefore, differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions) have been described in section 4.8 of the SmPC and specific monitoring has been included in section 4.4 of the SmPC. In addition, new information on these risks will be presented in future PSURs, stratified by age.

The MAH also took the opportunity to update the information on the paediatric population in Section 4.8 of the SmPC; the summary of the safety profile in 2 studies (Study MYC2190 and Study MYCS2675) conducted in paediatric renal transplant patients was updated. These studies were previously submitted and assessed in variation EMEA/H/C/00082/II/0027. This was endorsed by the CHMP. In addition, upon CHMP request, the adverse reactions occurring more frequently in the paediatric renal transplant patients study were summarised in a table in section 4.8 of the SmPC.

The MAH also presented data from the safety database on off-label use of MMF in paediatric RTx patients below 2 years of age. From the limited analysis presented, it seems that the infections and respiratory events are up to 4 times more frequent in RTx patients below 2 years of age in comparison to older age

groups. Due to small numbers, this should be interpreted with caution. Nethertheless, the increased occurrence of infections and respiratory events in the new paediatric population has been described in the SmPC.

As fatal cases of overdoses occurred in paediatric patients, the MAH updated section 4.9 to inform the prescribers of this risk.

At the time of approval of Cellcept in 1996, no RMP was required for registration. At the PRAC request, the MAH submitted an RMP to follow the known and new associated risks with Cellcept use. The known important identified risk Adverse pregnancy outcomes including Teratogenicity and Mutagenicity has been included in the RMP. And a new missing information was added: Long term safety (growth retardation, pubertal maturation and fertility, bone health, metabolic problems and neurocognitive development). The MAH will submit annual report to follow more closely the paediatric patients.

2.5.2. Conclusions on clinical safety

The safety profile in paediatric RTx patients 2 years and above forms the basis of safety profile expected in paediatric LTx and HTx patients and in paediatric population with RTx below 2 years (at starting dose of 600 mg/m2 of mycophenolate mofetil orally twice daily and maintenance dose of 900 mg/m2 twice).

Extrapolation of the safety profile (at starting dose of 600 mg/m2 of mycophenolate mofetil orally twice daily and maintenance dose of 900 mg/m2 twice daily) from RTx indication to other paediatric indications and younger subsets is supported by literature references and RWD.

Differences between age and transplant groups have been described in the SmPC to inform the prescriber as well as experience with medication errors have been reflected in the SmPC.

Uncertainties regarding long term safety are handled in the RMP and annual report will be submitted to closely follow this.

Overall mycophenolate mofetil has shown a well known and acceptable safety profile.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH was requested to submit an RMP with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

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

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 1.2 with the following content:

Safety concerns

Summary of safety concerns

Important identified risks	Adverse pregnancy outcomes including Teratogenicity and Mutagenicity
Important potential risks	None
Missing information	Long term safety (growth retardation, pubertal maturation and fertility, bone health, metabolic problems and neurocognitive development)

Pharmacovigilance plan

There are no additional pharmacovigilance activities.

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Pregnancy Adverse Effects including Teratogenicity and Mutagenicity	**Routine risk communication:** • Section 4.3 of the EU SmPC Contraindications • Section 4.4 of the EU SmPC Special warnings and precautions for use • Section 4.6 Pregnancy & Lactation • Section 4.8 of the EU SmPC: Undesirable effects **Legal status:** CellCept is a prescription only medicine **Additional risk minimization measures:** HCP Guide Patient Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Pregnancy Guided Questionnaires and enhanced follow up process **Additional pharmacovigilance activities:** None
Long term safety (growth retardation, pubertal maturation and fertility, bone health, metabolic problems and neurocognitive development)	**Routine risk communication:** Section 4.4 of the EU SmPC: Special warnings and precautions for use Section 4.8 of the EU SmPC: Undesirable effects **Legal status:** CellCept is a prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Annual safety reports Frequency: Yearly **Additional pharmacovigilance activities:** None

EU SmPC=European Union Summary of Product Characteristics; HCP=Healthcare Professional.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.2, 5.3 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and Excipients guideline which were reviewed and accepted by the CHMP.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable. The updates in the SmPC sections with this variation does not lead to substantial changes in the PL and therefore it is accepted that a user test is not performed.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The purpose of solid organ transplantation is to restore organ function, thereby prolonging the life of the adult or child. Solid organ transplantation is considered a life-saving and definitive therapy for adults and children who are suffering from end-stage organ failure due to a variety of causes. The model of alloimmune response, involving both naïve and memory lymphocytes, in the rejection of transplanted organs has been described in detail in the literature (Halloran et al. 2004). Rejection episodes are not an organ-specific complication and can occur for any transplanted organ. Additionally, there is little evidence to suggest that the mechanism of rejection is different in adults compared with children. Immunosuppression therapy is used to prevent rejection of the donor organ thereby enabling organ and patient survival.

3.1.2. Available therapies and unmet medical need

Immunosuppression is commonly separated into induction therapy (given at time of transplant), maintenance therapy (chronic medications), and acute rejection therapy (for the treatment of acute complications).

International Guidelines on Heart Transplant Guidelines for immunosuppression regimens specific to children are very limited. The ISHLT 2010 includes some recommendations specific to paediatric patients. Throughout these guidelines, most recommendations only receive an evidence level of C, based on consensus, due to the absence of randomised controlled clinical trials (Costanzo et al. 2010).

The International Guidelines on Liver Transplant (ILTS) 2019 Guidelines (adults and children) highlight the absence of robust studies for children but highlight the need for consensus-based guidelines to address the unique considerations in treating children, related to variations in growth and development, disease states, adherence, and risks of long-term exposure to IS. Paediatric-specific guidelines were developed by American Association for the Study of Liver Diseases and American Society of Transplantation in 2013. They make the case that for children there is no standard of care regimen, however, the current practice includes CNI based regimens (mainly TAC) as it avoids gingival hyperplasia and hirsutism associated with CsA. The use of MMF or mTOR inhibitors may enable reductions in steroid use and high dose CNI (Kelly et al. 2013).

CellCept is used off-label in the paediatric population with liver and heart transplants and most maintenance immunosuppressive protocols in children are similar to the protocols used in adults and employ a three-drug regimen consisting of a calcineurin inhibitor (CNI) (such as Cyclosporin A (CsA) or tacrolimus (TAC)), an antimetabolite agent (mycophenolate mofetil (MMF) or less commonly azathioprine

(AZA)), and tapering doses of glucocorticoids over the first year post transplantation (Kobashigawa et al. 2006; Costanzo et al. 2010).

There is therefore a need for approved medicine for paediatric transplantation.

3.1.3. Main clinical studies

Knowledge about the use of MMF in the adult reference populations of RTx, HTx, and LTx transplant patients and in paediatric RTx patients has been used to extrapolate to the target paediatric HTx and LTx populations.

Only one clinical study including nine paediatric patients undergoing liver transplantation was submitted to support the extension of indication. The remaining evidence is coming from published literature and previously submitted studies in RTx patients.

The clinical efficacy data to support the use of MMF in paediatric HTx and LTx come from available publications of studies conducted in the paediatric population, including 14 studies relevant to paediatric HTx and 15 studies relevant to paediatric LTx patients.

3.2. Favourable effects

Mycophenolic acid (MPA) acts as a selective, uncompetitive and reversible inhibition of inosine monophosphate dehydrogenase (IMPDH) and through the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. This is independent of transplant type and can be transferred from HTx and LTx and RTx to one another.

In addition, data generated in Roche-sponsored studies and available in the literature show that there is no difference in the mean PK characteristics of MMF/MPA in paediatric transplant patients across the age group of 1-18 years. At the recommended dosage, the same therapeutic target exposure is reached independent of patient age.

The clinical efficacy data to support the use of MMF in paediatric HTx and LTx from the above-mentioned publications of studies conducted in the paediatric population may confirm the efficacy observed in adults. The studies consistently suggest a benefit for MMF over AZA. Available evidence suggests that like adults, regimens containing MMF are effective and, compared to regimens containing AZA, they result in improved renal function, allowing CNI and steroid dose reductions and therefore reduction in the incidence of acute rejection in paediatric patients.

3.3. Uncertainties and limitations about favourable effects

The paediatric extrapolation approach utilized is based on PK-comparison with the adult reference population, under the assumption that a similar exposure produces a similar efficacy. The approach is supported by one paediatric clinical study in liver transplant patients, study PA16497, previously submitted paediatric clinical studies in renal transplant patients and by published studies from the literature.

The published supporting studies are largely observational over a period of time, too small in sample size, and not designed to demonstrate the efficacy of MMF. They typically include MMF together with other therapeutic agents as a part of the immunosuppressive regimen, and it is therefore not possible to directly link or attribute any of the observed outcomes to MMF.

Furthermore, very few of the publications retrieved are prospective studies; most studies are retrospective comparisons of transplant outcomes in the years before the introduction of MMF versus outcomes in the years after the inclusion of MMF in standard of care immunosuppressive regimens.

Therefore, although the studies consistently suggest a benefit for MMF, the impact of improved surgical and medical management is also likely to have influenced these findings.

However, all these additional data are only supportive. Since extrapolation from adults to children has been demonstrated, clinical efficacy is considered demonstrated.

Initially the MAH applied for an extension of indication in paediatric patients down to 3 months, however only limited data were available for infants (3 months to 1 year) and there was not enough data to support the justification for the PK comparability of MMF/MPA in infants and the proposed dosing regimen in this population. Therefore, the MAH proposed to include patients from 1 year instead of 3 months. This was considered acceptable by the CHMP. Indeed, PK comparability of MMF/MPA in children from 1 to 18 years has been demonstrated for RTx, LTX and HTx and the recommended paediatric dosing regimen in children from 1 to 18 years has been justified.

3.4. Unfavourable effects

Based on the review of the available published studies and post-marketing reports, the type and frequency of the reported adverse reactions in hepatic and cardiac transplant patients and renal patients below 2 years of age were consistent with those observed in paediatric and adult patients following renal transplant. No new safety signals have been identified. A few imbalances have been observed and described in the SmPC. Long-term safety has been identified as a missing information in the RMP and will be followed-up in the post-marketing setting.

3.5. Uncertainties and limitations about unfavourable effects

No new studies were performed in paediatric patients, therefore the safety profile in this new population is extrapolated from the known safety profile in paediatric RTx patients aged 2 years and older, and from other doses and indications as many of the supportive literature references lack the specific exposure or age groups.

From the limited analysis presented, it seems that the infections and respiratory events are up to 4 times more frequent in RTx patients below 2 years of age in comparison to older age groups. Due to small numbers this should be interpreted with caution. However, the increased occurrence of infections and respiratory events in this new paediatric population has been adequately described in the Section 4.8 of the SmPC.

Neoplasms Benign, Malignant and Unspecified, Gastrointestinal Disorders, and Blood and Lymphatic System Disorders were more frequent in paediatric HTx and LTx patients in comparison to adult groups. Similarly, differences in adverse events were observed between paediatric HTx and LTx patients in comparison to paediatric RTx group. These differences have been described and reflected in section 4.4 and 4.8 of the SmPC.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Knowledge about the use of CellCept/MMF in the adult reference populations of RTx, HTx, and LTx transplant patients and in paediatric RTx patients has been used to extrapolate to the target paediatric HTx and LTx populations.

PK comparability of MMF/MPA in children from 1 to 18 years has been demonstrated for RTx, LTX and HTx. The recommended paediatric dosing regimen in children from 1 to 18 years has been justified, so in conclusion, the pharmacokinetic data provided supports the approval of the application for use of MMF in children from 1 year to 18 year for all 3 types of transplantation.

The safety profile of MMF for the suggested dosing scheme and HTx-LTx indications in paediatric population is extrapolated from paediatric RTx patients who are 2 years and above to paediatric LTx and HTx patients. The safety profile (at starting dose of 600 mg/m2 of mycophenolate mofetil orally twice daily and maintenance dose of 900 mg/m2 twice daily) is similar to the known safety profile of the substance and no new safety signals were identified.

3.6.2. Balance of benefits and risks

The PK data support an extrapolation down to one year of age. The MAH initially proposed an extrapolation down to 3 months of age. However, there was not enough data to support the extrapolation to the infant population (3 months to 1 year). Therefore, the MAH decided to revise the indication to include children from the age of 1 year, this is agreed by the CHMP. The dosing regimen for this new population will be the same as for paediatric RTx patients above 2 years of age, with the possibility to increase the dose to 2g for paediatric RTx and 3g for paediatric LTx and HTx, in line with the adult indication.

Whilst some differences were seen in the paediatric population compared to the adult population, the overall safety profile appears generally consistent between paediatrics and adults. Adequate warnings regarding blood and lymphatic disorders and gastrointestinal disorders have been implemented in section 4.4 of the SmPC. No new safety signals were identified.

3.7. Conclusions

The overall B/R of Cellcept is positive in the following indication:

CellCept is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adult and paediatric (1 to 18 years of age) patients receiving allogeneic renal, cardiac or hepatic transplants.

4. Recommendations

Outcome

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

Variations accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	Type IB	I, II and IIIB

C.I.6.a: Extension of indication to include paediatric patients (1 year to 18 years of age) for hepatic and cardiac transplants and to extend the indication for renal transplants for paediatric patients starting from 1 year, based on pharmacokinetic data, published literature and the Roche Global Safety Database. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.2, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated accordingly. Version 1.2 of the RMP has also been approved.

Type IB (C.I.z): Update of the precautions to be taken before handling or administering the medicinal product in section 4.2 of the SmPC for the CellCept 500 mg tablets formulation in order to be in line with the other CellCept formulations. The Package Leaflet is updated to cross reference section 2 in section 6 for sodium content, in line with the QRD guidance.

In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and bring the PI in line with the latest QRD template version 10.3.

The group of variations leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I, II and IIIB are recommended.

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

Risk management plan (RMP)

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

In addition, an updated RMP should be submitted:

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

Additional risk minimisation measures

The Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the

programme, with the National Competent Authority.

The educational programme is aimed at ensuring that the health professionals and patients are aware of the teratogenicity and mutagenicity, the need for pregnancy tests before starting therapy with CellCept, the contraceptive requirements for both male and female patients and what to do in case of pregnancy during treatment with CellCept.

The MAH shall ensure that in each MS where CellCept is marketed, all healthcare professionals and patients who are expected to prescribe, dispense or use CellCept are provided with the following educational package:

· Physician educational material

· Patient information pack

The health professional educational material should contain:

· The Summary of Product Characteristics

· Guide for healthcare professionals

The patient information pack should contain:

· The Package Leaflet

· Guide for patients

The educational materials shall contain the following key elements:

Separate guides for healthcare professionals and patients should be provided. For patients, the text should be appropriately separated for men and women. The following areas should be covered in these guides:

- An introduction in each guide will inform the reader that the purpose of the guide is to tell them that a foetal exposure must be avoided and how to minimise the risk of birth defects and miscarriage associated with mycophenolate mofetil. It will explain that although this guide is very important it does not provide full information on mycophenolate mofetil and that the SmPC (healthcare professionals) and package leaflet (patients) supplied with the medicine must also be read carefully.

- Background information on mycophenolate mofetil teratogenicity and mutagenicity in humans. This section will provide important background information concerning the teratogenicity and mutagenicity of mycophenolate mofetil. It will provide details about the nature and magnitude of the risk, in line with the information provided in the SmPC. The information provided in this section will facilitate a correct understanding of the risk and explain the rationale for the following pregnancy prevention measures. Guides should also mention that patients should not give this drug to any other person.

- Counselling of patients: This section will emphasise the importance of a thorough, informative and ongoing dialogue between patient and healthcare professional about the pregnancy risks associated with mycophenolate mofetil and the relevant minimisation strategies including alternative treatment choices, if applicable. The need to plan a pregnancy will be highlighted.

- The need to avoid foetal exposure: Contraceptive requirements for patients of reproductive potential prior to, during and after treatment with mycophenolate mofetil. Contraceptive requirements for sexually active male patients (including vasectomised men) and female patients of childbearing potential will be explained. The need for contraception prior to, during and after treatment with mycophenolate mofetil, including details of the duration of time for which contraception must be continued after cessation of therapy, will be clearly stated.

In addition, the text relating to women should explain the pregnancy test requirements prior to and during therapy with mycophenolate mofetil; including the advice for two negative pregnancy tests prior to starting therapy and the importance of the timing of these tests. The need for subsequent pregnancy tests during treatment will also be explained.

- Advice that patients should not donate blood during therapy or for at least 6 weeks following discontinuation of mycophenolate mofetil. Furthermore, men should not donate semen during therapy or for 90 days following discontinuation of mycophenolate mofetil.

- Advice on action if a pregnancy occurs or is suspected during or shortly after being treated with mycophenolate mofetil. Patients will be informed that they should not stop taking mycophenolate mofetil but must contact their doctor immediately. It will be explained that the correct course of action, based on an assessment of the individual benefit-risk, will be determined on a case-by-case basis through a discussion between the treating physician and the patient.

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