NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	050722/S-049 and S-051 CellCept capsules 050723/S-049 and S-051 CellCept tablets 050758/S-047 and S-049 CellCept intravenous 050759/S-054 and S-056 CellCept for oral suspension
Priority or Standard	Standard
Submit Date(s)	9/10/2021
Received Date(s)	9/10/2021
PDUFA Goal Date	7/10/2022
Division/Office	Division of Rheumatology and Transplant Medicine
Review Completion Date	6/4/2022
Established/Proper Name	Mycophenolate mofetil
(Proposed) Trade Name	Cellcept
Pharmacologic Class	Immunosuppressant
Code name	
Applicant	Roche c/o Genentech
Dosage form	Capsules, tablets, oral suspension, solution for injection
Applicant proposed Dosing Regimen	600 mg/m^2 orally twice daily (starting dose) up to a maximum of 900 mg/m^2 twice daily (3 g or 15 mL of oral suspension)
Applicant Proposed Indication(s)/Population(s)	Prophylaxis of organ rejection in pediatric recipients of allogenic heart or liver transplants
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	213148006 Transplanted organ rejection (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Prophylaxis of organ rejection in pediatric recipients of allogenic heart or liver transplants
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Transplanted organ rejection
Recommended Dosing Regimen	600 mg/m^2 orally twice daily (starting dose) up to a maximum of 900 mg/m2 twice daily (3 g or 15 mL of oral suspension)

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

AC	advisory committee
ADL	activities of daily living
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNI	calcineurin-inhibitor
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CsA	cyclosporine
CS	corticosteroids
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IMPDH	inosine monophosphate dehydrogenase
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities

MMF	mycophenolate mofetil
mITT	modified intent to treat
MPA	mycophenolic acid
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OPTN	Organ Procurement and Transplantation Network
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
SRTR	Scientific Registry of Transplant Recipients
TDM	therapeutic drug monitoring
TEAE	treatment emergent adverse event
USPI	United States Prescribing Information

1 Executive Summary

1.1. Product Introduction

CellCept® [mycophenolate mofetil (MMF)] is an antimetabolite immunosuppressant indicated for the prophylaxis of allograft rejection in adult kidney, heart or liver transplant recipients and in pediatric kidney transplant recipients in combination with other immunosuppressants. Although extensively used off-label as a component of the standard of care immunosuppressive therapy, currently CellCept is not approved for use in pediatric heart and pediatric liver transplant recipients.

Following administration, MMF is metabolized to the active moiety, mycophenolic acid (MPA), which selectively and reversibly inhibits (inosine monophosphate dehydrogenase) IMPDH, the committed step in de novo guanosine nucleotide biosynthesis. In this way, MMF leads to cell cycle arrest and disrupts T and B cell proliferation, since, unlike other cells, T and B cells cannot utilize nucleotide salvage pathways. CELLCEPT is available in the following dosage forms:

- Capsules, 250mg
- Tablets, 500mg
- For oral suspension, powder for reconstitution (200 mg/mL after reconstitution)
- For injection, 500 mg single dose vial for intravenous (IV) administration

CellCept was first approved in the United States for the prophylaxis of organ rejection in kidney transplant recipients as an oral capsule formulation on May 3, 1995 (NDA 50-722). Subsequently, oral tablet, intravenous (IV) injection, and 'for oral suspension' formulations were approved for use on June 19, 1997, August 12, 1998, and October 1, 1998, respectively. CellCept was approved for use in adult heart transplant recipients on February 3, 1998 and in adult liver transplant recipients on July 28, 2000. CellCept was approved for the prophylaxis of organ rejection in pediatric kidney transplant patients 3 months of age and older on December 20, 2000.

The Applicant was released of its commitment to study the IV formulation in pediatric patients in June 2000. On June 7, 2000 the Applicant submitted a letter to the Agency documenting a telephone conversation that they did not intend to pursue the IV formulation for pediatric use and requested to be released from the post-marketing commitment (PMC) to study this formulation. The Agency agreed.

Since its initial FDA approval in 1995, CellCept has been approved in 119 countries worldwide and multiple generics are available in the U.S. market. The approval of CellCept in pediatric kidney transplant recipients was supported by evidence from adequate and well-controlled studies of MMF in adults with additional data from one open-label, pharmacokinetic (PK) and safety study of MMF in pediatric recipients of allogeneic kidney transplants in 2000.

Premise of the current sNDA:

The two new indications pursued in the current sNDAs, pediatric heart transplantation and pediatric liver transplantation meet the definition of rare diseases. The Orphan Drug Act (the ODA) generally defines a rare disease or condition as one affecting fewer than 200,000 people in the United States and per the Scientific Registry of Transplant Recipients (SRTR) data, the annual number of transplantations have been approximately 500 for each of these pediatric indications over the course of recent years.[1] Per the 2019 SRTR/OPTN data, 509 pediatric heart transplants and 551 pediatric liver transplants were performed in 2019 in the U.S..

Roche-Genentech, LLC pursued this sNDA in response to a December 2018 request from the Agency to add pediatric heart and pediatric liver transplant indications to the labeling. The current supplemental NDAs (sNDA) 50-722/s-049 (NDA 50-723/s-049, NDA 50-758/s-047, NDA 50-759/s-054) were submitted by the Applicant to update the CellCept® labeling by adding these two new indications. The current sNDA is based on the premise that the pathophysiology, diagnosis, and treatment of allograft rejection are sufficiently similar between the approved and proposed populations to permit extrapolation from the approved populations to the new pediatric populations.

As further explained under the Conclusions on the Substantial Evidence of Effectiveness section below, per the the 2019 FDA guidance on Substantial Evidence for Effectiveness, section IV. C, "In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials."[2]

Please note that since no clinical studies other than the early terminated PK and safety study in pediatric liver transplant recipients (Study PA 16497), were submitted with this application, several sections of this Unireview are not completed as they are not applicable.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted this sNDA to add the pediatric heart and pediatric liver transplant indications to CellCept labeling in response to a 2018 request from the Agency.

The 2019 FDA guidance on Substantial Evidence for Effectiveness, section IV.C, states:

> "The rule revising the Pediatric Use section of product labeling (21 CFR 201.57(f)(9)(iv)) makes allowance for inclusion of pediatric use information in labeling without controlled clinical trials of the use in children. In such cases, a sponsor must provide other information to support pediatric use, and the Agency must conclude that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit extrapolation from adult efficacy data to pediatric patients. Evidence that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes evidence of common pathophysiology

> and natural history of the disease in the adult and pediatric populations, evidence of common drug metabolism and similar concentration-response relationships in each population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions."[1]

The premise of this application is based on the fact that the mechanism of transplant organ rejection is similar across different organs, both in adults and children, and that similar drug exposure in pediatric patients as in adults will lead to the same therapeutic effect (i.e., a reduction in the risk of acute rejection).

This sNDA relies on the following for substantial evidence of effectiveness:

- The mechanism of rejection is similar across all organs and age groups
- The extrapolation of efficacy from the pivotal studies for the approved adult indications (Studies ICM 1866, MYC023, and MYC022 in Adult Kidney Transplant; Study MYCS 1865 in Adult Heart Transplant; Study MYCS2646 in Adult Liver Transplant)
- The extrapolation of efficacy from the approved pediatric kidney transplant indication (supported by the pediatric kidney transplantation studies MYC 2190 and MYCS 2675).
- The ontogeny of IMPDH (target of MPA) is suggested to be complete by 2 years of age. It is unclear whether there may be ontogenetic differences in IMPDH in children younger than 2 years of age that would impact MPA activity in this age group. See section 6.2 for detailed information and discussion.
- Evidence of efficacy from published literature of the use of CellCept in pediatric heart and pediatric liver transplant recipients
- Supporting data from the Scientific Registry of Transplant Recipients (SRTR)/ Organ Procurement and Transplantation Network (OPTN) database
- One PK study in pediatric liver transplant recipients (PA 16497)

Summary of Dosing Rationale

(See Clinical Pharmacology section 6 of this review for detailed dosing rationale information).

The proposed oral MMF dosing regimen for pediatric heart transplant and liver transplant patients is a starting dose of 600 mg/m^2 up to a maximum of 900 mg/m^2 twice daily (BID). The proposed dosing parallels the recommended oral MMF dosage in adult kidney transplant patients (1 g BID) relative to that for adult heart transplant and liver transplant patients (1.5 g BID).

The dosing rationale for this sNDA is primarily based on established exposure relationships among the approved adult and pediatric populations derived from information in these prior approval packages. For pediatric liver transplant recipients, support is also derived from exposure matching based on a comparison of PK derived from study PA 16497 with PK in the approved populations as well as the published literature data. The available clinical pharmacology data demonstrates that PK relationships across pediatric transplant populations

are similar to those observed across adult transplant populations.

In pediatric kidney transplant patients 3 months of age and older, the recommended oral dosage of 600 mg/m^2 BID was derived based on achieving the same MPA AUC_{0-12} as that in adult kidney transplant patients administered 1 g BID of MMF. The proposed maximum dosage of 900 mg/m^2 BID represents a 50% increase over the minimum dosage and arithmetically matches the increase in the dosage recommended for adult heart transplant and liver transplant patients. Based on the higher dosing needs in liver transplant patients, it is expected that MPA exposure in pediatric liver transplant patients at a dose of 900 mg/m^2 will be within the range of observed exposures in pediatric kidney transplant patients at a dose of 600 mg/m2.

The rationale for increasing MMF dosage in the approved adult heart transplant population relative to the adult kidney transplant population is, heart transplant recipients generally require more potent immunosuppression. MPA PK after MMF dosing in adult liver transplant patients was also noted to be lower than that in adult kidney transplant patients at the same dose. As a result, liver transplant patients were noted to have higher dosing needs to achieve similar MPA exposure to that in adult kidney transplant patients.

For pediatric patients aged 3 months to 2 years of age, there is limited PK data. In addition, there is information suggesting there are ontogenetic changes in IMPDH and deficient activity of uridine diphosphate glucuronosyltransferase (UGT) enzymes in this age group with a potential impact to MPA disposition. IMPDH is the MPA target enzyme and UGT is responsible for glucuronidation to MPAG in the liver. It is unclear what impact ontogenetic changes in IMPDH and deficient UGT may have on MPA activity in children younger than 2 years of age.

However, as stated in section 6.1 of this Unireview, “Based on the PK data in pediatric kidney transplant patients, no age-related trend in exposure was observed with comparable exposure across age groups achieved by the same BSA based dosing regimen.” Though information in patients less than 2 years of age is limited, published literature provides supportive evidence of efficacy for both the pediatric heart and pediatric liver transplant indications. Also, the SRTR data indicate that approximately 90% of pediatric heart and 50% of pediatric liver transplant immunosuppression (IS) regimens contain MMF. These SRTR reports note excellent 1 year and 5 year graft outcomes with >90% survival at 1 year and >80% survival at 5 years for both the pediatric heart and pediatric liver transplant populations.[3,4]

With evidence of excellent graft and patient outcomes across a wide range of doses reported in the published literature submitted in support of this sNDA, a range between 600 and 900 mg/m^2 is acceptable from the Clinical perspective and in concurrence with Clinical Pharmacology reviewer’s conclusions.

DPMH Consultation
DRTM consulted the Division of Pediatric and Maternal Health (DPMH) and the Pediatric

Research Committee (PeRC) on the above review strategy and dosing rationale. PeRC and DPMH agreed that the efficacy of MMF can be extrapolated from the approved adult and pediatric indications to pediatric heart transplant and pediatric liver transplant patients. DPMH and PeRC accepted the premise that the pathophysiology, diagnosis, and management of allograft rejection are sufficiently similar between different solid organs and between adults and children. Both PeRC and DPMH agreed there is acceptable evidence to support dosing recommendations for pediatric patients 3 months and older. PeRC agreed with DRTM's decision to add this new PK data and the new indications of pediatric heart and pediatric liver transplantation to the CellCept® labeling.

Conclusion:

The SRTR data indicates that MMF is widely used off-label in pediatric heart and pediatric liver transplant recipients as part of the standard of care (SOC) immunosuppressive regimens and has replaced azathioprine as the anti-metabolite of choice in clinical practice. The use of CellCept in pediatric heart transplant and pediatric liver transplant patients is supported by adequate and well-controlled studies and pharmacokinetic data in adult heart transplant and liver transplant patients. Additional supportive data include pharmacokinetic data in pediatric kidney transplant and pediatric liver transplant patients and published evidence of clinical efficacy and safety in pediatric heart transplant and pediatric liver transplant patients.

The clinical pharmacology review strategy to support the recommended dosing is based on established PK relationships across the approved adult kidney, heart, and liver transplant populations and the pediatric kidney transplant population. For pediatric liver transplant patients, Study PA 16497 provides PK information that allows a comparison of exposures with PK in the approved populations. For pediatric heart transplant recipients, support for approval is provided from the literature. Additional supportive information in the form of patient and graft survival outcomes in pediatric heart and pediatric liver transplant recipients treated with MMF containing immunosuppressive regimens is provided from the SRTR databases. For both pediatric indications, support is also provided from the published literature.

Though there is limited PK data in pediatric patients 3 months to 2 years of age and, despite concerns about the ontogeny of IMPDH and deficient UGT below the age of two, there is adequate published evidence (including SRTR data) that MMF containing immunosuppressive regimens have resulted in successful clinical outcomes in pediatric heart and pediatric liver recipients who are 3 months old and above. These outcomes are similar to those seen in the corresponding adult transplant populations.

Recommendation: The evidence submitted with this sNDA supports the approval of CellCept for use in pediatric heart and pediatric liver transplant recipients for the prophylaxis of organ rejection.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

CellCept® has been on the U.S. market for 26 years. For pediatric heart and pediatric liver transplantation in particular, SRTR/OPTN data indicate the rising use of MMF in immunosuppressive (IS) regimens since 2012 with almost 90 % of pediatric heart transplant patients and almost 50 % of liver transplant recipients on an MMF containing regimen in 2019. Outcomes are also noted to be very good. For example, five-year graft survival rates for pediatric liver transplant and pediatric heart transplant patients transplanted in 2014 were reported to be higher than than 80% across all pediatric age groups. One and five year patient survival rates among pediatric liver transplant patients is comparable to the same survival rates in adults. Survival in pediatric heart transplant recipients is better than adults at 10 years post-transplant (81.8% vs 60.5%). Similarly, for pediatric heart transplant patients, 5 year survival for patients transplanted between 2012-2014 was higher than 80%. Notably, the death rate in children at 10 years post heart transplant was lower at 28.7% compared to approximately 40% for adults.[2,3] Although the increasing use of MMF-containing regimens cannot be the sole basis of these comparable and better outcomes, it does suggest a benefit for the use of MMF in immunosuppressive regimens.

CellCept was approved for use in pediatric kidney transplant recipients in 2000. As noted above, CellCept is already widely used off-label in the majority of pediatric heart and pediatric liver transplant recipients. Approval of CellCept in these two new pediatric transplant populations will likely enhance reimbursement and improve access for pediatric heart and liver transplant recipients.

Despite these benefits, in general all immunosuppressive therapies including MMF are associated with an increased risk of infections and malignancies. Patients taking immunosuppressants such as MMF, are at increased risk of developing opportunistic infections, which can be serious, and malignancies particularly lymphomas, skin cancer, and post-transplant lymphoproliferative disorder (PTLD). In the benefit/risk considerations of immunosuppressive treatment for transplant recipients, the risk of malignancies, infections and other adverse drug reactions are weighed against the benefit of preventing rejection and maintaining the life-sustaining transplanted organ. Without heart or liver transplantation and accesss to drugs to maintain these organs, many pediatric patients with end-stage heart or liver disease have limited survival and poor quality of life since alternative heart replacement and liver replacement therapies do not provide comparable outcomes to that of transplantation and may not be available for every patient. In this regard, CellCept has demonstrated a favorable benefit/risk ratio from prior trials in the approved adult and pediatric transplant populations, from published literature in the proposed populations, and from more than 20 years of U.S. postmarketing experience.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Analysis of Condition	• Per the 2019 SRTR / OPTN Data:
	  • Approximately 500 pediatric heart transplantations and 500 pediatric liver transplantations are performed annually in the United States (U.S.).
	  • In more than 90% of pediatric heart transplant recipients and in 50% of pediatric liver transplant recipients an MMF containing IS regimen is utilized.
	  • For pediatric heart transplant recipients transplanted from 2012-2014, 1-year and 5-year patient survival rates were reported as 92% and 84%, respectively. For pediatric liver transplant recipients transplanted from 2012-2014, 1-year survival rate was more than 90% and 5-year survival rate was 89%.
		• Pediatric heart transplantation and pediatric liver transplantation offer improved survival to pediatric patients with end-stage heart disease (ESHD) and end-stage liver disease (ESLD) who otherwise have limited treatment options
		
		• MMF, in combination with concomitant IS agents, and other advances in transplantation has contributed to excellent pediatric patient and graft survival with comparable outcomes to adults.

	• There is limited PK data for pediatric patients less than 2 years of age • It is unclear if ontogenetic changes in IMPDH (the MPA target) occur in patients under 2 years of age • According to literature data, UGT is deficient at birth and absent in the fetal liver. It is unclear to what extent deficient UGT activity contributes to differences in MPA exposure in children less than 2 years of age	• Based on the PK data in pediatric kidney transplant patients, no age-related trend in exposure was observed with comparable exposure across age groups on the same BSA based dosing regimen. • Overall, the proposed initial dose of 600 mg/m^2 may be appropriate in this age group based on prior approval in pediatric kidney transplant recipients aged 3 months and older.
	• High inter-individual variability of MPA was noted from PK in the approved populations and from the PK study in pediatric liver transplant patients, PA 16497. The Applicant proposed (b) (4)	• (b) (4) Agency did not agree with the Applicant's proposal

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		• Given that MMF is already used off-label in pediatric heart transplant and pediatric liver transplant recipients, the proposed labeling for patients aged 3 months to less than 2 years of age will permit maximum flexibility based on current use in clinical practice.
Current Treatment Options	• Per the 2019 SRTR/OPTN data, for pediatric heart and pediatric liver transplant patients, the three most common maintenance IS regimens are tacrolimus (tac)+ MMF, tac + MMF + steroids, and tac + steroids • Please see table under section 2.2 for additional treatment options	• MMF has been widely used off-label in combination with other IS agents in pediatric heart and pediatric liver transplant rejection prophylaxis and this approval is expected to improve access for patients
Benefit	• CellCept has been approved in adult kidney, heart, liver and pediatric kidney transplant populations and has demonstrated efficacy in maintaining these transplanted organs for these populations. • CellCept has been on the U.S. market for 26 years with multiple generics approved • Pediatric heart and pediatric liver transplants are performed in patients with limited alternative treatment options for end-stage heart disease (ESHD) and end-stage liver disease (ESLD), and the organs are life-sustaining for these patients. • CellCept is already used off label for both indications	• Since its initial approval in 1995, MMF has become more commonly used in IS regimens for all solid organ transplantations including almost 90% of pediatric heart transplant IS regimens and 50% of pediatric liver transplant IS regimens. • Transplant outcomes have steadily improved with 5 year graft survival at >80% for both pediatric heart and pediatric liver transplant recipients with transplants from 2014. • As described in the Benefit-Risk Summary and Assessment above, 10 year patient survival is better for pediatric heart transplant and pediatric liver transplant recipients compared to their adult counter parts.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Most common risks associated with CellCept include myelosuppression, risk of infection, gastrointestinal toxicities and embryo-fetal toxicity • The safety profile observed in the studies conducted by the Applicant for the currently approved indications and in the published literature do not raise new safety concerns. • There is a possibility of discovering new adverse drug reactions after increased usage due to new marketing, however, there are no uncertainties based on the current available data.	• The safety profile of CellCept is well established and the risks noted are already described in the labeling • There is already a REMS in place for mycophenolate products for the prevention/ mitigation of potential embryo-fetal toxicity. Please see CellCept USPI section 8 for reference to REMS and for a Risk Summary. • A review of safety from the approved pediatric kidney transplant studies (MYC 2190, MYCS 2675), the pediatric liver transplant PK Study (PA 16497), published literature and the Applicant's post-marketing safety database did not raise new safety concerns.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☒	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Heart transplantation and liver transplantation are lifesaving therapeutic options that give children a second chance with a reasonable quality of life. In contrast to kidney transplant, where patients have a readily available therapeutic option of renal replacement therapy, pediatric patients with end-stage heart disease (ESHD) or end-stage liver disease (ESLD) have limited options that can provide a reasonable quality of life. Patients who undergo heart or liver transplantation require medications to maintain their allografts, which are life sustaining.

Heart and liver transplantation are both rare conditions with 509 pediatric heart transplant surgeries and 551 pediatric liver transplant surgeries performed in 2019. SRTR/OPTN data indicate that in 2019 more than 90% of heart transplant center regimens used an MMF containing immunosuppression (IS) regimen and close to 50% of liver transplant centers used MMF in there IS regimen.

In addition, outcomes are excellent with 1 year and 5 year patient survival among pediatric heart transplant recipients from 2012-2014 at 92% and 84%, respectively. For pediatric liver transplant recipients from 2012-2014, 1 year survival was also more than 90% and 5 year survival was 89%. In comparison, for adult heart transplant recipients aged 18-64 years and transplanted between 2012-2014, 1 year survival was >90% and 5 year survival was >77%. For adult liver transplant recipients aged 18-64 years with deceased donor liver transplants from 2012-2014, 1 year patient survival was >90% and 5 year survival was approximately 80%.[2,3] These outcomes are due to various factors including improvements in surgical techniques and donor-recipient matching; nonetheless, one of these factors is also the introduction of MMF into the IS regimen.

2.2. Analysis of Current Treatment Options

The following products for use in kidney transplant recipients as induction, or maintenance immunosuppressants have been approved. The wording from sections of the package inserts are provided below.

Table 1. Approved Agents for Induction Treatment

Approved Agents for Induction Treatment				
Product name	**Relevant Indication**	**Year of Approval**	**MOA**	**Dosing/Administration**
Thymoglobulin ® (rabbit derived anti-thymocyte globulin)	Prophylaxis and treatment of acute rejection (AR) in kidney transplant patients in conjunction with concomitant immunosuppression	1998	Polyclonal antilymphocyte preparation with unknown MOA. Possible mechanisms include T cell clearance from circulation and modulation of T cell activation, homing, and cytotoxic activities	IV: prophylaxis of AR- 1.5 mg/kg of body weight administered daily for 4-7 days Treatment of AR: 1.5 mg/kg of body weight administered daily for 7-14 days
Simulect ® (basiliximab)	Prophylaxis of acute organ rejection in kidney transplant patients in combination with CsA and corticosteroids (CS)	1998	Chimeric (murine/human) monoclonal antibody (ab) (IgG1k) to IL-2Rα (also known as CD25 antigen on the surface of activated T cells)	IV: 20 mg x 2 doses; first dose within 2 hours of transplant surgery and second dose within 4 days after transplantation.
Zenapax® (Daclizumab)	Prophylaxis of acute rejection in kidney transplant recipients as part of a combined immunosuppressive regimen that includes CsA and CS	1997, discontinued in 2009 due to low market use / demand and alternative treatment available	Chimeric (murine/ human) monoclonal Ab (IgG1k) to IL-2Rα (CD25 antigen)	IV: 1.0 mg/kg mixed with 50 mL sterile 0.9% sodium chloride solution and administered over 15 min x 5 doses over 14 day intervals

Table 2. Drugs Used Off Label for Induction Treatment

Drugs Used Off Label For Induction Treatment				
Product name	**Relevant Indication**	**Year of Approval**	**MOA**	**Dosing/Administration**
Campath® (alemtezumab)	Treatment of B-cell chronic lymphocyte leukemia (B-cell CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy	2001	Cytolytic antibody against CD52 on B and T cells, monocytes, macrophages, NK cells and a subpopulation of granulocytes	IV: 30 mg/1 mL IV infusion over 2 hours. Gradually escalate to maximally recommended dose of 30 mg in 3-7 days
Atgam® (Equine anti-thymocyte globulin)	Treatment of kidney transplant rejection	1981	Not determined. Composed of antibodies that bind to a variety of proteins on the surface of lymphocytes and depletes circulating T cells	IV: 10 to 15 mg/kg daily IV for 14 days; additional alternate-day therapy up to a total of 21 doses may be given
Orthoclone® OKT3 (muromonab-CD3) (first monoclonal ab approved for use in humans)	Treatment of acute rejection in kidney transplant and steroid resistant acute rejection in heart and liver transplant	1986, withdrawan from market in 2010 due to adverse effects, better alternatives, and reduced usage	Monoclonal ab to CD3 receptor on T cells	IV: 5 mg/kg single bolus injection x 10-14 days No longer used

Table 3. Approved Maintenance Immunosuppression Agents

Approved Maintenance Immunosuppression Agents				
Product name	**Relevant Indication**	**Year of Approval**	**MOA**	**Dosing/Administration**
Prograf® (tacrolimus) and generics	For the prophylaxis of organ rejection in adult and pediatric patients receiving allogeneic liver, kidney, heart, or lung transplants in combination with other immunosuppressants (IS)	1994	(CNI) Binds to FKBP-12 protein forming a complex of tac-FKBP-12, calcium, calmodulin, and calcineurin and inhibits activity of calcineurin. Net result is inhibition of T-lymphocyte activation, proliferation and B-cell response	IV, PO: oral capsule, oral suspension: .075 mg/kg/day every 12 hours – 0.3 mg/kg/day every 12 hours Dosing varies according to concomitant IS and time post-transplant. Therapeutic drug monitoring (TDM) is recommended
Astagraf XL® (tacrolimus extended release capsules)	For the prophylaxis of organ rejection in adult and pediatric kidney transplant recipients who can swallow capsules intact and in combination with other IS	2013	Same as for prograf	PO: capsule: 0.15-0.2 mg/kg once daily prior to reperfusion or within 48 hrs of transplant. Not interchangeable with other tacrolimus products. Dosing varies according to concomitant IS and time post-transplant. TDM is recommended

Product name	Relevant Indication	Year of Approval	MOA	Dosing/Administration
Envarsus XR® (extended release (ER) tablets)	For the prophylaxis of organ rejection in de novo kidney transplant patients or kidney transplant patients converted from tacrolimus immediate-release formulations in combination with other IS	2015	Same as for prograf	PO: ER tablets: De-novo: 0.14 mg/kg/day Conversion: 80% of the pre-conversion dose of tacrolimus immediate release. Not interchangeable with other tacrolimus products. Dosing varies according to time post-transplant. TDM recommended
Neoral® (cyclosporine, (CsA)) and generics	For the prophylaxis of organ rejection in kidney, liver, and heart transplant patients in combination with azathioprine and CS	1983	(CNI) a cyclic polypeptide that forms a complex with cyclophilin to block the phosphatase activity of calcineurin, which in turn decreases the production of inflammatory cytokines by T-lymphocytes	PO: gelatin capsule, oral solution 7-9±3 mg/kg/day, dosing dependent on type of transplant and time post-transplant TDM is recommended.

Product name	Relevant Indication	Year of Approval	MOA	Dosing/Administration
Myfortic® (mycophenolic acid)	For the prophylaxis of organ rejection in adult and pediatric (at least 5 years old and 6 months post-transplant) of kidney transplant patients, in combination with CsA and CS	2004	Anti-metabolite. Uncompetitive and reversible inhibitor of IMPDH. It is the active moiety of MMF.	PO: Delayed-release tablets. Not interchangeable with MMF tablets and capsules. 720 mg twice daily for adults In children 5 years of age and older (at least 6 months post-transplant): 400 mg/m^2
Nulojix® (belatacept) (biologic)	For prophylaxis of organ rejection in adult patients receiving a kidney transplant in combination with basiliximab induction, MMF, and CS	2011	A selective T-cell costimulation blocker that binds to CD80 and CD86 on antigen presenting cells, thereby blocking CD 28 mediated costimulation of T cells	IV: Initial: 10 mg/kg starting day of transplantation , then Day 5, end of week 2, week 4, week 8, and week 12 after transplant. Maintenance: 5 mg/kg end of week 16, and every 4 weeks

Product name	Relevant Indication	Year of Approval	MOA	Dosing/Administration
Rapamune® (sirolimus)	For the prophylaxis of organ rejection in kidney transplant patients 13 years or older in combination with CsA and CS. CsA withdrawal recommended for low-moderate immunologic risk patients, but has not been established in high immunologic risk patients	1999	mTOR inhibitor: binds to FKBP-12 protein and inhibits mammalian target of rapamycin (MTOR) and suppresses T cell proliferation	PO: Tablets, oral solution Initial dose is 2 mg/day to to achieve trough concentrations between 5-15 ng/mL. TDM is recommended

Product name	Relevant Indication	Year of Approval	MOA	Dosing/Administration
Zortress® (everolimus)	Prophylaxis of organ rejection in adult kidney (low-moderate immunologic risk) in combination with basiliximab, CsA (reduced doses), and CS. In liver transplant patients (no earlier than 30 days post-transplant) in combination with tacrolimus and CS	2009	mTOR inhibitor (same as Rapamune)	PO: Tablets Starting dose: 0.75 mg twice daily -1 mg twice daily to achieve target trough concentration. TDM is recommended.
Imuran® (azathioprine) and generics	For prophylaxis of organ rejection in kidney transplant patients	1968	Anti-metabolite. Imidazolyl derivative of 6-mercaptopurine that inhibits purine synthesis and causes T cell suppression	PO: Tablet Initial dose-3-5 mg/kg/day, maintenance dose -1-3 mg/kg/day. CBC monitoring important to monitor for bone marrow toxicity

Table 4. Drugs Used Off Label as Maintenance Immunosuppression Agents

Drugs Used Off Label as Maintenance Immunosuppression Agents				
Product name	**Relevant Indication**	**Year of Approval**	**MOA**	**Dosing/Administration**
Prednisone (Corticosteroids (CS))	Indicated for use in primary or secondary adrenocortical insufficiency and multiple autoimmune and inflammatory conditions	1955	synthetic glucocorticoid used for its anti-inflammatory effects in disorders of many organ systems	PO: Tablets Variable dosing

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

CellCept was first approved in the U.S. on May 3, 1995 for the prophylaxis of organ rejection in adult kidney transplant recipients. CellCept was then approved for the prophylaxis of organ rejection in adult heart transplant recipients on February 11, 1998 followed by approval in adult liver transplant recipients on July 28, 2000. On December 20, 2000, the FDA approved CellCept for the prophylaxis of organ rejection in pediatric kidney transplant recipients. In addition to the oral capsule formulation, CellCept has been approved for the same indications in tablet form, oral suspension, and as an intravenous solution. Thereafter, CellCept was marketed and approved in 119 countries worldwide. Multiple generics have also been approved since 2008.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) of 2003, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. PREA applied retroactively to applications submitted on or after April 1, 1999.

Thus, PREA applies to the liver transplant indication (approved on July 28, 2000), but PREA does not apply to the kidney transplant (approved on May 3, 1995) and the heart transplant indications (approved on February 11, 1998) as they were approved before the retroactive date of April 1, 1999. The pediatric kidney transplant indication was approved under a PMR commitment stated in the adult kidney transplant approval letter to continue studies in pediatric populations that would further characterize the PK of MMF and its metabolites and the activity of MPA after IV and oral administration. The PK Study (PA 16497) in pediatric liver transplant recipients fulfills the PMC described in the adult liver transplant approval letter. The Applicant was released of the pediatric liver PMC on October 25, 2009 The Applicant was released of their commitment to assess the IV formulation in a pediatric population based upon a June 7, 2000 communication (see section 1.1 for details).

As evident from the regulatory history, CellCept has been on the U.S. market for 26 years. It has been used in combination with other immunosuppressive agents in the majority of solid organ transplant recipients, not only for the approved indications, but for off-label use in populations other than solid organ transplant recipients as well.

3.2. Summary of Presubmission/Submission Regulatory Activity

There were several communications with the Applicant prior to this supplemental NDA submission. In December 2018, the Agency reached out to the Applicant and requested that the Applicant consider updating CellCept labeling to add indications for the prophylaxis of organ

rejection in pediatric heart and liver transplant rejection. After several communications regarding the content of the sNDA, the Agency agreed with the Applicant's proposed approach to extrapolate efficacy and PK from the approved indications to the proposed indications with safety evidence from published literature and SRTR/OPTN data. The Applicant submitted a pre-sNDA meeting request in March 2021, and written responses (WRO) were conveyed to the Applicant on June 17, 2021 indicating agreement with the overall format and content of the sNDA. The sNDA application was subsequently submitted on September 10, 2021.

In regard to prior PMCs and PMRs, the following information is noted. The July 28, 2000 approval Letter of CellCept for use in adult liver transplant recipients contained the following post-marketing commitment (PMC):

> "You will conduct an appropriate study or studies on the pharmacokinetics and safety of CellCept in pediatric liver transplant recipients less than 12 years old, especially pediatric patients less than 3 years old with biliary atresia."

There were no PMCs are discussed in the February 11, 1998 approval letter for Cellcept for the adult heart transplant indication. The May 3, 1995 adult kidney transplant approval letter for CellCept highlights the following PMC:

> "Please continue current studies in pediatric populations. In addition, studies which would further characterize the pharmacokinetics of mycophenolate mofetil and its metabolites after the administration of I.V. and oral formulations, as well as activity of MPA from these formulations, should be undertaken in the pediatric populations."

The December 20, 2000 pediatric kidney transplant approval letter for CellCept states, "the above commitment to study CellCept oral formulations in pediatric patients undergoing renal transplantation was fulfilled. Your ongoing commitment to evaluate the pharmacokinetics, metabolism, and activity of CellCept® Intravenous in the pediatric population is the subject of a separate letter to NDA 50-758."

In regard to the PMC pertaining to the IV formulation, the Applicant submitted a June 7, 2000 letter documenting a telephone conversation with the Agency in which the Applicant stated they did not intend to complete this PMC as the pivotal study in pediatric kidney transplant patients (MYCS 2675) did not include patients who were dosed with the IV formulation. The Applicant's letter states:

> "Following a telephone call from Mr. Matt Bacho on June 6, 2000, we are hereby submitting a confirmation that Roches does not intend to supplement the NDA for CellCept Intravenous for the Pediatric Use of CellCept. Therefore, Roche is herein requesting a waiver for submitting a cross-reference supplemental application to the CellCept Intravenous NDA 50-758."

The Applicant's request for release from the IV formulation PMR was granted as of June 7, 2000.

The Division presented both the pediatric heart transplant and pediatric liver transplant

indication proposals in the current submission to the Pediatric Research Committee (PeRC) on February 22, 2022 because both were submitted under one sNDA. The PeRC agreed on the Division's review strategy, the decision to grant a waiver for the 0-3 month age group, and the release of the Applicant from the commitment to study the IV formulation in pediatric patients.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

As there are no source data available for the clinical studies, OSI did not recommend any inspections.

4.2. Product Quality

Not applicable (N/A)

4.3. Clinical Microbiology

N/A

4.4. Devices and Companion Diagnostic Issues

N/A

5 Nonclinical Pharmacology/Toxicology

N/A

6 Clinical Pharmacology

6.1. Executive Summary

Mycophenolate mofetil (MMF) (CELLCEPT®) is a prodrug of mycophenolic acid (MPA), a small molecule inhibitor of inosine monophosphate dehydrogenase (IMPDH), an important enzyme in the *de novo* guanosine biosynthesis pathway. Because lymphocytes cannot generate guanosine via salvage pathways and therefore rely on the *de novo* pathway, MPA inhibition of IMPDH can induce cytostatic effects on lymphocytes and inhibit proliferative responses.

MMF oral capsules were originally approved in 1995 for the prophylaxis of organ rejection in adult recipients of allogeneic kidney transplants in combination with other immunosuppressants (NDA 050722). Since its initial approval, MMF has been approved for additional indications, including for prophylaxis of organ rejection in adult recipients of allogeneic heart (050722/S-002, 1998) and liver (050722/S-005, 2000) transplants, as well as in pediatric recipients of allogeneic kidney transplants (050722/S-007, 2000) in patients aged 3 months and older. The approved oral dosage for adult kidney, heart, and liver transplant recipients is 1 g twice daily (BID), 1.5 g BID, and 1.5 g BID, respectively. The approved oral dosage in pediatric patients aged 3 months and older is 600 mg/m^2 BID.

The currently approved Cellcept has age appropriate oral formulation for pediatric patients aged 3 months and older. Cellcept is available for oral administration as capsules (NDA 050722) containing 250 mg of MMF, tablets (NDA 050723) containing 500 mg of MMF, and as a powder for oral suspension (NDA 050759) which, when reconstituted, contains 200 mg/mL of MMF. CELLCEPT Intravenous (NDA 050758) is also available under the same label.

The goal of the present efficacy supplement (NDA 050722/S-049, 050723/S-049, NDA 050759/S-054) is to add indications for the prophylaxis of organ rejection in pediatric heart and liver transplant recipients aged 3 months and older. NDA 050758/S-047 Cellcept IV labeling supplement was also submitted to align label. The submission was provided in response to FDA's request to the Applicant in 2018 to update the CellCept labeling to include information on pediatric liver and heart transplant patients. The Applicant's proposed dosing regimen for pediatric heart and liver transplant recipients aged 2 years and older is 600 mg/m^2 orally BID up to a maximum of 900 mg/m^2 BID (3 g or 15 mL of oral suspension). It is also proposed that pediatric patients with body surface area (BSA) ≥ 1.25 m^2 may initiate therapy using capsules or tablets at a fixed dosage in a manner identical to that for the approved pediatric renal

transplant indication. For pediatric patients below 2 years of age, no specific dosage was provided, but it is proposed that higher doses may be required to achieve a plasma exposure of 30 to 60 mcg*h/mL, particularly when cyclosporine A is administered concomitantly. The proposed starting dosage of 600 mg/m^2 BID is the same dosage approved for pediatric kidney transplant recipients aged 3 months and older. The maximum proposed dosage of 900 mg/m^2 BID is a 50% increase from the initial 600 mg/m^2 BID dosage and mimics the recommended increase in dosage seen in adult indications between kidney transplant recipients (1 g BID) and heart and liver transplant recipients (both 1.5 g BID).

The clinical pharmacology submission content of the application includes study reports from previously submitted clinical studies in pediatric kidney transplant recipients (Studies MYC 2190 and MYCS 2675), a study report and dataset from a pharmacokinetic study in pediatric liver transplant recipients completed in 2005 (Study PA 16497), a narrative summary of MPA clinical pharmacokinetics based on data obtained in adult and pediatric patients, and a summary of available data in the published literature. No new studies were conducted to evaluate MPA clinical pharmacology in pediatric heart and liver transplant recipients. In addition, no clinical studies have been conducted in pediatric heart transplant recipients. MPA clinical pharmacology in this population is primarily derived from two published retrospective analyses.

The review strategy to support efficacy and the proposed dosing is based on extrapolation from pediatric kidney, and adult kidney, heart, and liver transplant recipients. Established PK relationships among these populations are derived from information in prior approval packages. For pediatric liver transplant recipients, support is also derived from exposure matching based on a comparison of PK derived from Study PA 16497 with PK in approved populations. For pediatric heart transplant recipients, supportive evidence is provided from the literature. Safety data is established in pediatric kidney transplant patients at a dose of 600 mg/m^2 BID. Clinical pharmacology data can therefore also be used to provide evidence to support safety of the proposed dosing in pediatric heart and liver transplant patients based on the observed MPA PK relationships among all pediatric populations. The key clinical pharmacology findings are summarized below:

- With respect to efficacy and dosing in pediatric liver transplant patients, the proposed initial dose of 600 mg/m^2 with increases up to 900 mg/m^2 is acceptable in pediatric liver transplant recipients aged 3 months and older. A comparison of dose-normalized (to 600 mg/m^2) MPA AUC values in 12 pediatric kidney transplant patients less than 6 years of age at 9 months post-transplant with those values in 7 pediatric liver transplant patients [median age 17 months (range: 10 – 60 months)] and at 6 months and beyond post-transplant revealed that, at the same dose, there were on average 23% lower AUC values in the pediatric liver compared to pediatric kidney patients. This is consistent with the need of higher dosing in adult liver transplant patients compared to kidney transplant patients to achieve the same exposure. Therefore, the efficacy of Cellcept in pediatric liver transplantation could be extrapolated from adult transplantation based on the comparable Cellcept exposure.

- With respect to efficacy and dosing in pediatric heart transplant patients, the proposed initial dose of 600 mg/m^2 with increases up to 900 mg/m^2 is acceptable in pediatric heart transplant recipients aged 3 months and older. In adult transplant patients administered the same dosage of CELLCEPT, there is similar MPA exposure among kidney transplant and heart transplant patients. Based on the established similarity in MPA exposure between pediatric kidney transplant and adult kidney transplant patients at their respective approved doses, it is expected that MPA exposure at the recommended dosage will be similar in pediatric heart transplant and adult heart transplant patients. Therefore, the efficacy of Cellcept in pediatric heart transplantation could be extrapolated from adult heart transplantation data based on the estimated comparable Cellcept exposure.

- For dosing regimen in patients 3 month-< 2 years of age, there is limited PK data for pediatric patients < 2 years of age and information suggesting there are ontogenetic changes occurring at that stage of life with potential impacts to MPA disposition. Based on the PK data in pediatric kidney transplant patients, no age-related trend in exposure was observed with comparable exposure across age groups achieved by the same BSA based dosing regimen. There is no evidence that higher dose is required for patients <2 years of age. Overall, the proposed initial dose of 600 mg/m^2 may be appropriate in this age group based on prior approval in pediatric kidney transplant recipients aged 3 months and older.

- Clinical pharmacology does not agree with the Applicant's proposal (b) (4) Given that MMF is already used off-label in pediatric heart transplant and liver transplant recipients, the proposed labeling for patients aged 3 months to < 2 years of age will permit maximum flexibility based on current use in clinical practice.

- Regarding potential DDI with cyclosporine A when administered concomitantly, the review team acknowledges that cyclosporine is known to interfere with enterohepatic recirculation and overall decreases MPA exposure. As this DDI is not unique to pediatric liver or heart transplant patients, the statement is added to Section 7 of the label.

- With respect to safety in pediatric liver transplant patients, safety data is established in pediatric kidney transplant patients at a dose of 600 mg/m^2 BID. Based on MPA PK relationships across pediatric transplant populations, CellCept 900 mg/m^2 is expected to achieve comparable exposure in pediatric liver transplant patients as the exposure in pediatric kidney transplant patients with the approved 600 mg/m^2 dose. Therefore, the safety of CellCept up to the proposed maximum dose of 900 mg/m^2 in pediatric liver

transplant recipients could be leveraged from the safety data in pediatric kidney transplant patients.

- With respect to safety in pediatric heart transplant patients, safety data is established in pediatric kidney transplant patients at a dose of 600 mg/m^2 BID. Based on MPA PK relationships across pediatric transplant populations, CellCept 600 mg/m^2 is expected to achieve comparable exposure in pediatric heart transplant patients as the exposure in pediatric kidney transplant patients with the approved 600 mg/m^2 dose. Therefore, the safety of CellCept up to the dose of 600 mg/m^2 in pediatric heart transplant recipients could be leveraged from the safety data in pediatric kidney transplant patients. The available safety database in kidney transplant patients is insufficient to support the safety of the 600-900 mg/m^2 dose in heart transplant patients. Evidence for safety of the 600-900 mg/m^2 dose in pediatric heart transplant recipients is derived from available clinical data and post-marketing safety reports. Please see the clinical review in Section 8.2 for additional information.

Recommendation: From a clinical pharmacology perspective, the data provided in this NDA supplement support approval of MMF for use in pediatric heart transplant and liver transplant recipients aged 3 months and older.

Post-marketing requirement/Post-marketing commitment: None.

6.2. Summary of Clinical Pharmacology Assessment

The clinical pharmacology assessment was based on review of MPA clinical pharmacokinetics in approved populations (pediatric kidney, and adult kidney, liver, and heart transplant recipients), a pharmacokinetic study in pediatric liver transplant recipients completed in 2005 (Study PA 16497), and supportive evidence from the literature.

6.2.1. Pharmacology and Clinical Pharmacokinetics

A brief summary of the pharmacokinetics of MMF and MPA is given below. Refer to the approved labeling for CellCept for a more detailed description of the pharmacology and clinical pharmacokinetics of MMF and MPA.

Per the approved labeling for CellCept, after oral administration, MMF undergoes complete conversion to MPA, the active metabolite. The mean absolute bioavailability of oral MMF relative to IV MMF was 94%. The area under the plasma-concentration time curve (AUC) for MPA appears to increase in a dose-proportional fashion in kidney transplant patients receiving multiple oral doses of MMF up to a daily dose of 3 g (1.5 g twice daily).

In the early post-transplant period (less than 40 days post-transplant), kidney, heart, and liver transplant patients had mean AUCs approximately 20% to 41% lower and mean C_{max}

approximately 32% to 44% lower compared to the late post-transplant period (i.e., 3 to 6 months post-transplant). This is referred to as non-stationarity in MPA pharmacokinetics.

Metabolism of MMF to MPA occurs pre-systemically after oral dosing. MPA is metabolized principally by glucuronyl transferase to form MPA glucuronide (MPAG), which is not pharmacologically active. *In vivo*, MPAG is converted to MPA during enterohepatic recirculation. Due to the enterohepatic recirculation of MPAG/MPA, secondary peaks in the plasma MPA concentration-time profile are usually observed 6 to 12 hours post-dose.

At clinically relevant concentrations, MPA is 97% bound to plasma albumin. MPAG is 82% bound to plasma albumin at MPAG concentration ranges that are normally seen in stable kidney transplant patients; however, at higher MPAG concentrations, the binding of MPA may be reduced as a result of competition between MPAG and MPA for protein binding.

MPA PK in Adult Transplant Populations

Table 5 illustrates MPA PK behavior across all adult populations in the early and late post-transplant periods, including high variability in MPA exposure. Data also indicate that MPA AUC_{0-12} in adult kidney transplant patients receiving 1 g BID is approximately 33% lower relative to that in adult heart transplant patients receiving 1.5 g BID in the early post-transplant period. On the other hand, MPA AUC_{0-12} in adult kidney transplant patients receiving 1 g BID is approximately similar to that in adult liver transplant patients receiving 1.5 g BID in the early post-transplant period. Lastly, MPA exposure in the late post-transplant period is increased relative to the early post-transplant period for all adult populations, demonstrating non-stationarity in MPA PK.

Table 5. MPA AUC0-12 [mean ± SD] in the early and late post-transplant periods following administration of multiple doses of MMF to adult kidney, heart, and liver transplant patients.

Adult Patient Population	Oral BID Dose	Early Post-Transplant MPA AUC_{0-12} (mcg*h/mL)	Late Post-Transplant MPA AUC_{0-12} (mcg*h/mL)
Kidney Transplant	1 g	27.3 ± 10.9 to 32.9 ± 15.0	65.3 ± 35.4
Heart Transplant	1.5 g	43.3 ± 20.8	54.1 ± 20.4
Liver Transplant	1.5 g	29.2 ± 11.9	49.3 ± 14.8

(*Source: Reviewer-generated table adapted from the approved CellCept labeling, Roche 2021*)

MPA PK in Pediatric Kidney Transplant Patients

MPA PK behavior in pediatric kidney transplant patients receiving oral MMF at a dosage of 600 mg/m^2 BID (up to a maximum of 1 g BID) is similar to adult kidney transplant patients receiving 1 g BID. Data in **Table 6** show early and late post-transplant MPA AUC_{0-12} dose-adjusted to 600 mg/m^2 in pediatric kidney transplant patients, separated by age group. MPA AUC_{0-12} values in pediatric kidney transplant patients match what is observed in adult kidney transplant patients. Non-stationarity in MPA PK is also observed in pediatric patients just as it is in adults.

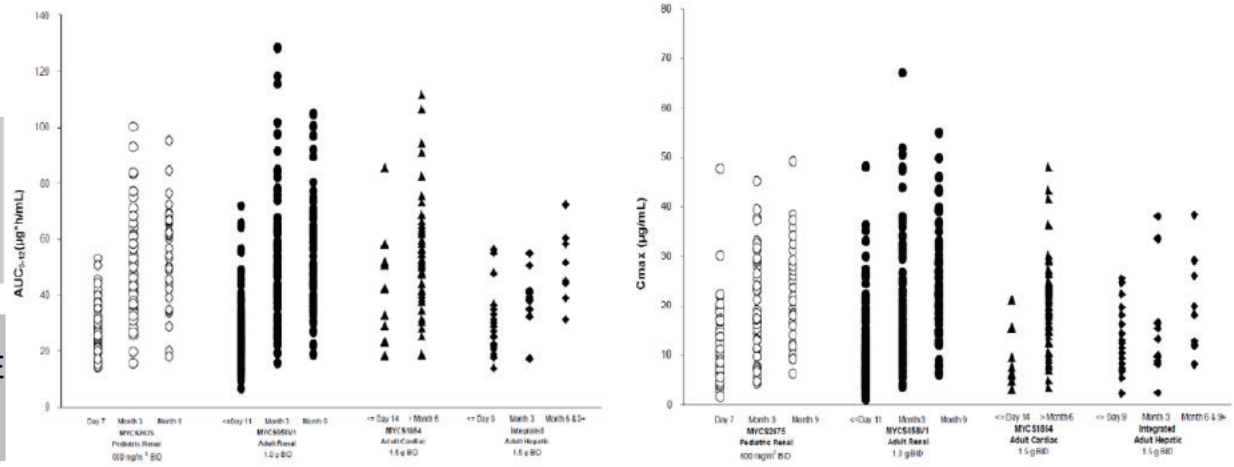
Table 6. Dose-adjusted MPA AUC0-12 [mean ± SD] by age group in the early and late post-transplant periods following administration of multiple doses of MMF to pediatric kidney transplant patients

Age Group	Early Post-Transplant Dose-Adjusted* MPA AUC_{0-12} (mcg*h/mL)	Late Post-Transplant (Month 3) Dose-Adjusted* MPA AUC_{0-12} (mcg*h/mL)	Late Post-Transplant (Month 9) Dose-Adjusted* MPA AUC_{0-12} (mcg*h/mL)
1 to < 2 years	22.5 ± 6.66	47.4 ± 14.7	55.8 ± 11.6
1 to < 6 years	27.4 ± 9.54	49.7 ± 18.2	61.0 ± 10.7
6 to < 12 years	33.2 ± 12.1	61.9 ± 19.6	66.8 ± 21.2
12 to 18 years	26.3 ± 9.14	53.6 ± 20.3	56.7 ± 14.0

*AUC_{0-12} values are adjusted to a dose of 600 mg/m^2
(*Source: Reviewer-generated table adapted from the approved CellCept labeling, Roche 2021*)

MPA PK at a dosage of 600 mg/m^2 BID in pediatric kidney transplant patients is also similar to adult heart and liver transplant patients, as shown by overlap in individual values for AUC_{0-12} and C_{max} (**Figure 1**).

Figure 1. Comparison of individual MPA AUC0-12 (left) and Cmax (right) across studies in pediatric kidney, and adult kidney, heart, and liver transplant patients.



AUC_{0-12h}=area under the concentration-time curve from Time 0 to 12 hours; b.i.d.=twice a day.
Source: Roche Report P-180594.

b.i.d.=twice a day; C_{max}=maximum concentration.
Source: Roche Report P-180594.

Note on the legend: Open circles – pediatric kidney transplant (600 mg/m^2 BID); black circles – adult kidney transplant (1 g BID); black triangles – adult heart transplant (1.5 g BID); black diamonds – adult liver transplant (1.5 g BID)
(*Source: Summary of Clinical Pharmacology, pages 79-80, module 2.7.2, NDA 50722/S-049, SDN 1050, submitted Sept. 10, 2021*)

MPA PK in Pediatric Liver Transplant Patients

MPA PK data in pediatric liver transplant patients is primarily derived from Study PA 16497, an uncontrolled, open-label study designed to predict the MMF dose that would yield an MPA AUC_{0-12} of 58 mcg*h/mL in pediatric liver transplant patients in the late post-transplant period (> 6 months post-transplant). PK data was determined in 7 patients aged 10 to 60 months. **Table 7** compares MPA PK determined in pediatric liver transplant patients with that observed in pediatric renal transplant patients. Of note, the pediatric renal transplant data shown are in subjects < 6 years of age and at 9 months post-transplant.

Table 7. Comparison of MPA and MPAG AUC_{0-12} and Cmax normalized to a dose of 600 mg/m2 from pediatric liver and kidney transplant patients in the late post-transplant period.

MPA	**Liver (our study; n=7)**	**Kidney ([1]; n=12)**
Mean ± SD AUC_{0-12h} (µg.h/mL)	47.0 ± 21.8	60.9 ± 10.7
Mean ± SD C_{max} (µg/mL)	14.5 ± 4.21	30.4 ± 9.16
MPAG		
Mean ± SD AUC_{0-12h} (µg.h/mL)	[(a)]924 ± 341	453 ± 132
Mean ± SD C_{max} (µg/mL)	110 ± 45.6	64.8 ± 17.6

Note: (a) n=6 since MPAG AUC_{0-12h} was not calculable for Patient 2002

(*Source: Clinical Study Report for Study PA 16497, page 34, module 5.3.3.2, NDA 50722/S-049, SDN 1050, submitted Sept. 10, 2021*)

When normalized to the same dose, MPA AUC_{0-12} and C_{max} in pediatric liver transplant patients is lower relative to those observed in pediatric kidney transplant patients. This behavior mimics what is observed in adults in which MPA AUC_{0-12} in adult liver transplant patients is similar to that in adult kidney transplant patients when liver transplant patients receive a dose that is 50% greater. Per the approved labeling for CellCept, the mean ± SD MPA AUC_{0-12} and C_{max} in adult liver transplant patients > 6 months post-transplant receiving 1.5 g BID (n = 6) were 49.3 ± 14.8 mcg*h/mL and 19.3 ± 11.7 mcg/mL, respectively. This indicates that in the late post-transplant period, the MPA exposure achieved in pediatric liver transplant patients when normalized to a dose of 600 mg/m^2 is approximately equal to the MPA exposure achieved in adult liver transplant patients receiving 1.5 g BID.

MPA PK in Pediatric Heart Transplant Patients

The Applicant has not conducted any studies in pediatric heart transplant recipients. It is indicated that clinical pharmacology experience in this patient population is primarily derived from two published studies in the literature. Both studies include retrospective analyses of data in pediatric heart transplant patients and the primary information on MPA exposure is via serum trough MPA concentrations as opposed to MPA AUC_{0-12}. Study design details and subject-level data are not available for review. As a result, qualitative information derived from these publications is used as supportive evidence.

- Dipchand AI, Pietra B, McCrindle BW, et al. Mycophenolic acid levels in pediatric heart transplant recipients receiving mycophenolate mofetil. *J Heart Lung Transplant*. 2001;20(10):1035-43.
- Gajarksi RJ, Crowley DC, Zamberlan MC, Lake KD. Lack of correlation between MMF dose and MPA level in pediatric and young adult cardiac transplant patients: Does the MPA level matter? *Am J Transplant.* 2004;4(9):1495-1500.

Both studies describe MPA PK behavior in pediatric heart transplant patients, including high variability in PK, the need for higher doses in the early post-transplant period due to the non-stationarity in PK, and the need for lower doses when tacrolimus instead of cyclosporine is administered as the concomitant calcineurin inhibitor. These conclusions are general trends that have been observed with MMF use in other approved transplant populations and support that MPA PK behavior might be similar in pediatric heart transplant patients and other transplant populations. In addition, similar MPA trough concentrations were observed in children and adults receiving the same dose of MMF and concomitantly taking cyclosporine A (Gajarski *et al*., 2004), suggesting that MPA PK could be similar between pediatric and adult heart transplant patients.

The paper by Gajarski *et al*. reports the mean ± SD MPA trough concentration in pediatric heart transplant patients concomitantly taking cyclosporine as 1.6 ± 1.5 mcg/mL. MPA trough concentrations were determined for pediatric kidney transplant patients using data from Study MYCS 2675, the pivotal study used to support approval of MMF in this population. In the late post-transplant period (3 to 9 months post-transplant), the mean ± SD MPA trough concentrations ranged from 1.79 ± 1.74 to 1.92 ± 1.06 mcg/mL. The values are similar and suggest that MPA exposure may be similar among pediatric kidney and heart transplant patients.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed oral MMF dosing regimen for pediatric heart transplant and liver transplant patients is a starting dose of 600 mg/m^2 up to a maximum of 900 mg/m^2 BID. The proposed dosing parallels the recommended oral MMF dosage in adult kidney transplant patients (1 g BID) relative to that for adult heart transplant and liver transplant patients (1.5 g BID).

MPA PK following MMF dosing in heart transplant patients has been shown to be similar to that in kidney transplant patients. The rationale for increasing the MMF dosage in heart transplant patients relative to kidney transplant patients is to prevent loss of the graft. MPA PK after MMF dosing in liver transplant patients is lower than that in kidney transplant patients at the same dose. As a result, liver transplant patients have higher dosing needs to achieve similar MPA exposure to that in kidney transplant patients. The lower exposure provides the rationale for increasing the MMF dosage in liver transplant patients.

In pediatric kidney transplant patients 3 months of age and older, the recommended oral dosage of 600 mg/m^2 BID was derived based on achieving the same MPA AUC_{0-12} as that in adults following the 1 g BID regimen. The available clinical pharmacology data has provided evidence suggesting that PK relationships across pediatric transplant populations mimics those observed across adult transplant populations.

The proposed minimum dosage of 600 mg/m^2 BID has precedence as the recommended dosage in kidney transplant patients. The proposed maximum dosage of 900 mg/m^2 BID represents a 50% increase over the minimum dosage and arithmetically matches the increase in the dosage recommended for adult heart transplant and liver transplant patients. Based on the higher dosing needs in liver transplant patients, it is expected that MPA exposure in pediatric liver transplant patients at a dose of 900 mg/m^2 will be within the range of observed exposures in pediatric kidney transplant patients at a dose of 600 mg/m^2. Refer to the clinical review in Section 8.2 for discussion on the safety of the 900 mg/m^2 dose in pediatric heart transplant patients. Given the high inter-individual variability in MPA exposure after MMF dosing and the potential for increased adverse events at the highest dose, proposing a range between 600 and 900 mg/m^2 appears appropriate from a clinical pharmacology perspective.

Therapeutic Individualization

A specific dosing regimen has not been proposed for pediatric patients younger than 2 years of age. The Applicant has instead proposed (b) (4)

(b) (4)

(b) (4)

(b) (4) As a result, we do not agree with the Applicant's proposal (b) (4)

(b) (4)

Outstanding Issues

There is uncertainty regarding whether MPA exposure in patients younger than 2 years of age will match that observed in older pediatric patients due to ontogenetic differences in expression of enzymes important for MPA activity and disposition.

It is suggested that IMPDH, the MPA target, does not undergo ontogenetic changes in children 2 years of age and older based on a study analyzing IMPDH activity in peripheral blood mononuclear cells (PBMCs) in healthy children and adults[1]. Children under 2 years of age were not evaluated in this study, and no additional information has been provided to describe IMPDH expression and activity in this age group. It is therefore unclear whether there may be ontogenetic differences in IMPDH in children younger than 2 years of age that would impact MPA activity in this age group.

MPA plasma concentrations are dependent on metabolism via glucuronidation in the liver to MPAG, which leads to enterohepatic recirculation following MPAG secretion in bile and glucuronide cleavage. Based on literature sources provided by the Applicant, the activity of uridine diphosphate glucuronosyltransferase (UGT) enzymes is deficient at birth and absent from the fetal liver, but increases to reach adult levels by approximately 2 to 4 years of age.[2,3] It is unclear how and to what extent deficient UGT activity may contribute to differences in MPA exposure in children younger than 2 years of age.

Despite the potential differences in patients aged 3 months to 2 years of age, there is available data that suggests that MPA exposure may be similar in this age group as compared with older age groups. In pediatric kidney transplant patients, MPA AUC_{0-12} in patients under 2 years of age was numerically lower relative to older age groups. However, an analysis of MPA AUC vs. continuous age did not suggest an age-related trend in exposure. Overall, the 600 mg/m^2 BID dosage was approved in all pediatric kidney transplant patients down to 3 months of age. In

[1] Rother A, Glander P, Vitt E, *et al.* Inosine monophosphate dehydrogenase activity in paediatrics: age-related regulation and response to mycophenolic acid. *Eur J Clin Pharmacol*. 2012;68(6):913-922.
[2] Anderson GD. Developmental pharmacokinetics. *Semin Pediatr Neurol*. 2010;17(4):208-13.
[3] Miyagi SJ, Collier AC. Pediatric development of glucuronidation: the ontogeny of hepatic UGT1A4. *Drug Metab Dispos*. 2007;35(9):1587-92.

addition, in Study PA 16497 in pediatric liver transplant patients, most patients (6/8) were under 2 years of age. Despite high inter-patient variability in MPA exposure, mean MPA AUC_{0-12} was approximately equal to that achieved in adult liver transplant patients receiving 1.5 g BID.

Overall, the available data in pediatric kidney transplant and liver transplant patients suggests that MPA exposure after MMF dosing remains approximately consistent across pediatric patients, including those younger than 2 years of age, and adults. However, high inter-individual variability in exposure has been observed with MMF dosing, and, in current clinical use, the dose may be modified based on factors such as tolerability and concomitant medications. In the context of organ transplantation, the medical urgency necessitating use of MMF outweighs the potential uncertainty in MPA PK in patients younger than 2 years of age, which is not well described. Therefore, the proposed labeling for all patients, including those aged 3 months to < 2 years of age will permit flexibility in dosing at the clinician's discretion based on current use in clinical practice.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

PK Relationships in Adult Transplant Populations

MPA PK behavior across adult populations in both the early and late post-transplant periods is illustrated in **Table 8**. Among each transplant population, AUC_{0-12} increases in the late post-transplant period relative to the early post-transplant period, demonstrating the non-stationarity in MPA PK. In the early post-transplant period, MPA AUC_{0-12} in adult kidney transplant patients receiving 1 g MMF orally BID is approximately 33% lower relative to that in adult heart transplant patients receiving 1.5 g orally BID (27.3 to 32.9 vs. 43.3 mcg*h/mL). This decrease is consistent with a 33% decrease in the dose and suggests that MPA exposure would be similar among kidney and heart transplant patients at the same dose. MPA AUC_{0-12} in adult kidney transplant patients receiving 1 g orally BID is similar to that in adult liver transplant patients receiving 1.5 g orally BID (27.3 to 32.9 vs. 29.2 mcg*h/mL). This suggests that MPA exposure in liver transplant patients would be lower at the same dose and is the reason why the recommended MMF dosage in adult liver transplant patients is higher relative to that in adult kidney transplant patients.

Table 8. Pharmacokinetic parameters for MPA [mean ± SD] following administration of MMF to adult healthy volunteers (single dose), and adult kidney, heart, and liver transplant patients (multiple doses).

Healthy Volunteers	Dose/Route	T_{max} (h)	C_{max} (mcg/mL)	Total AUC (mcg•h/mL)
Single dose	1 g/oral	0.80 (±0.36) (n=129)	24.5 (±9.5) (n=129)	63.9 (±16.2) (n=117)
Kidney Transplant Patients (twice daily dosing) Time After Transplantation	**Dose/Route**	**T_{max} (h)**	**C_{max} (mcg/mL)**	**Interdosing Interval AUC(0-12h) (mcg•h/mL)**
5 days	1 g/iv	1.58 (±0.46) (n=31)	12.0 (±3.82) (n=31)	40.8 (±11.4) (n=31)
6 days	1 g/oral	1.33 (±1.05) (n=31)	10.7 (±4.83) (n=31)	32.9 (±15.0) (n=31)
Early (Less than 40 days)	1 g/oral	1.31 (±0.76) (n=25)	8.16 (±4.50) (n=25)	27.3 (±10.9) (n=25)
Early (Less than 40 days)	1.5 g/oral	1.21 (±0.81) (n=27)	13.5 (±8.18) (n=27)	38.4 (±15.4) (n=27)
Late (Greater than 3 months)	1.5 g/oral	0.90 (±0.24) (n=23)	24.1 (±12.1) (n=23)	65.3 (±35.4) (n=23)
Heart transplant Patients (twice daily dosing) Time After Transplantation	**Dose/Route**	**T_{max} (h)**	**C_{max} (mcg/mL)**	**Interdosing Interval AUC(0-12h) (mcg•h/mL)**
Early (Day before discharge)	1.5 g/oral	1.8 (±1.3) (n=11)	11.5 (±6.8) (n=11)	43.3 (±20.8) (n=9)
Late (Greater than 6 months)	1.5 g/oral	1.1 (±0.7) (n=52)	20.0 (±9.4) (n=52)	54.1[a] (±20.4) (n=49)
Liver transplant Patients (twice daily dosing) Time After Transplantation	**Dose/Route**	**T_{max} (h)**	**C_{max} (mcg/mL)**	**Interdosing Interval AUC(0-12h) (mcg•h/mL)**
4 to 9 days	1 g/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 g/oral	1.15 (±0.432) (n=20)	13.1 (±6.76) (n=20)	29.2 (±11.9) (n=20)
Late (Greater than 6 months)	1.5 g/oral	1.54 (±0.51) (n=6)	19.3 (±11.7) (n=6)	49.3 (±14.8) (n=6)

[a]AUC(0-12h) values quoted are extrapolated from data from samples collected over 4 hours.

(*Source: Approved CellCept labeling, Roche 2021*)

PK in Pediatric Kidney Transplant Recipients

MPA PK in pediatric kidney transplant recipients was also determined as part of the pediatric development program. Two studies were conducted and previously reviewed by the Agency: 1) MYC 2190, a dose-ranging pilot study to determine the MMF dose which would yield an MPA AUC_{0-12} of 27.2 mcg*h/mL, and 2) MYCS 2675, the pivotal phase 3 confirmatory study. These studies supported approval of MMF for the prophylaxis of organ rejection in pediatric recipients of allogeneic kidney transplants aged 3 months and older.

The goal of Study MYC 2190 was to determine the MMF dose that would deliver an MPA AUC_{0-12} of 27.2 mcg*h/mL in pediatric kidney transplant recipients. The early post-transplant target exposure of 27.2 was derived based on the results of a concentration-controlled trial conducted in adult kidney transplant recipients (MYC 058). Pediatric subjects (n = 40; age range: 1 to 18 years) were randomized to receive one of three oral MMF dose levels: 15, 23, or 30 mg/kg BID. Results from this trial suggested that the 23 mg/kg BID dose most closely achieved the target value of 27.2 mcg*h/mL. Due to high inter-subject variability in exposure, the Applicant performed additional analyses suggesting that BSA-based dosing reduced the coefficient of variation by approximately 10%. Linear regression analysis of MPA AUC versus dose using data from MYC 2190 and adult data led to the estimation that a BSA-based dose of 600 mg/m^2 provided an MPA AUC closest to the target exposure of 27.2. Thus, the 23 mg/kg dose was equated to a dose of 600 mg/m^2.

The 600 mg/m^2 dose was carried forward into Study MYCS 2675, the pivotal confirmatory study. Study MYCS 2675 was open-label and non-randomized. Pediatric kidney transplant recipients (n = 100; age range: 10 months to 18 years) received oral MMF at a dose of 600 mg/m^2 up to 1 g BID. PK was evaluated in a subset of 55/100 pediatric patients in the early post-transplant period (Day 7) and twice in the late post-transplant period (Month 3 and Month 9). PK results (**Table 9**) from this study indicate that an MPA AUC_{0-12} of approximately 27.2 mcg*h/mL was achieved in the early post-transplant period in pediatric kidney transplant recipients following a dose of 600 mg/m^2. In addition, exposure in pediatric kidney transplant recipients matches that achieved in adult kidney transplant recipients receiving a dose of 1 g BID. Lastly, PK results demonstrate that MPA exposure increases in the late post-transplant period relative to the early post-transplant period (non-stationarity in PK), a phenomenon observed in all adult populations.

Table 9. Computed MPA PK parameters by age group and time post-transplant in pediatric kidney transplant recipients receiving 600 mg/m2 (up to 1 g) BID MMF from Study MYCS 2675.

Age Group (n)	Time	T_{max} (h)	Dose Adjusted[a] C_{max} (mcg/mL)	Dose Adjusted[a] AUC_{0-12} (mcg•h/mL)
	Early (Day 7)			
1 to less than 2 yr (6)[d]		3.03 (4.70)	10.3 (5.80)	22.5 (6.66)
1 to less than 6 yr (17)		1.63 (2.85)	13.2 (7.16)	27.4 (9.54)
6 to less than 12 yr (16)		0.940 (0.546)	13.1 (6.30)	33.2 (12.1)
12 to 18 yr (21)		1.16 (0.830)	11.7 (10.7)	26.3 (9.14)[b]
	Late (Month 3)			
1 to less than 2 yr (4)[d]		0.725 (0.276)	23.8 (13.4)	47.4 (14.7)
1 to less than 6 yr (15)		0.989 (0.511)	22.7 (10.1)	49.7 (18.2)
6 to less than 12 yr (14)		1.21 (0.532)	27.8 (14.3)	61.9 (19.6)
12 to 18 yr (17)		0.978 (0.484)	17.9 (9.57)	53.6 (20.3)[c]
	Late (Month 9)			
1 to less than 2 yr (4)[d]		0.604 (0.208)	25.6 (4.25)	55.8 (11.6)
1 to less than 6 yr (12)		0.869 (0.479)	30.4 (9.16)	61.0 (10.7)
6 to less than 12 yr (11)		1.12 (0.462)	29.2 (12.6)	66.8 (21.2)
12 to 18 yr (14)		1.09 (0.518)	18.1 (7.29)	56.7 (14.0)

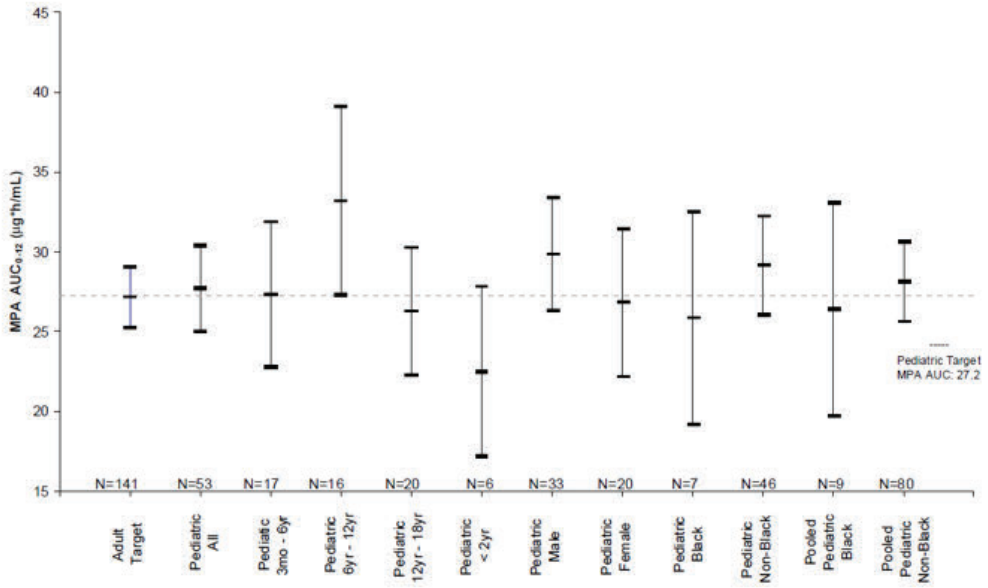
[a] adjusted to a dose of 600 mg/m^2
[b] n=20
[c] n=16
[d] a subset of 1 to <6 yr

(*Source: Approved CellCept labeling, Roche 2021*)

MPA PK parameters were similar across all age groups. In subjects < 2 years of age, the dose-adjusted MPA AUC_{0-12} was numerically, but not significantly, lower than that determined for all other age groups. This is likely due to the small sample size (n = 6) and high variability observed in calculated PK parameters. Of note, the subjects comprising the < 2 years age group are a subset of the subjects in the < 6 years age group. In addition, the mean dose-adjusted C_{max} in the oldest age group was numerically and significant lower at Months 3 and 9, respectively, which is also likely due to the wide PK variability observed.

Given the high variability in MPA PK, the Applicant undertook additional analyses to examine MPA AUC distribution by age group, sex, and race using data from Study MYCS 2675 (**Figure 2**). The overall distributions in **Figure 2** demonstrate that the 600 mg/m^2 yielded an AUC comparable to that observed in adults receiving a dosage of 1 g BID with exposure distributed around the target AUC of 27.2 (left two bars). When separated by age group, MPA AUC appeared numerically higher in the 6 to 12 years age group, and numerically lower in the < 2 years age group. No difference in exposure based on sex or race was apparent (right six bars).

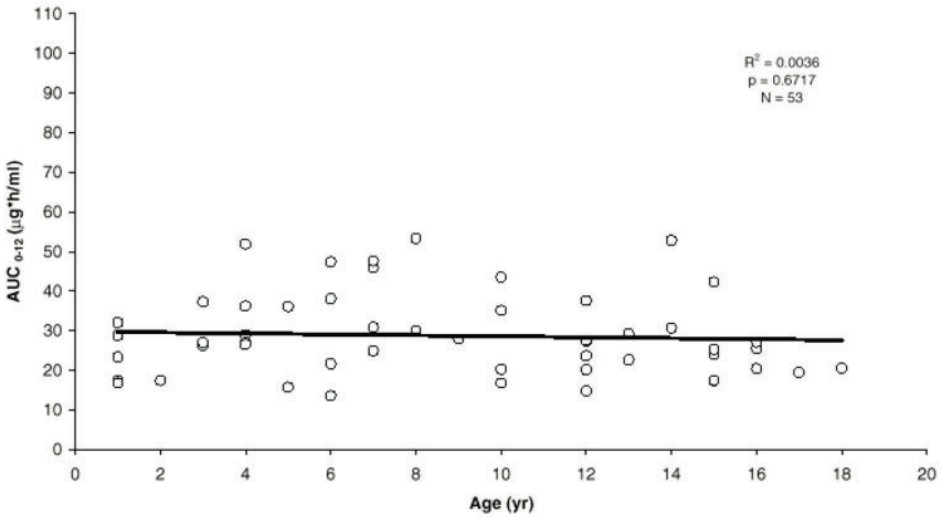
Figure 2. Dose-adjusted MPA AUC0-12 distribution by age group, sex, and race in pediatric kidney transplant recipients using data from Study MYCS 2675.



(*Source: Expert Report P-180603, page 53, module 5.3.3.2, NDA 50722/S-049, SDN 1050, submitted Sept. 10, 2021*)

To determine whether there may be any clinically significant changes in MPA exposure based on age, the Applicant examined MPA AUC_{0-12} vs. age as a continuous variable (**Figure 3**). Despite previous observations, data suggest that there is no age-related trend in exposure.

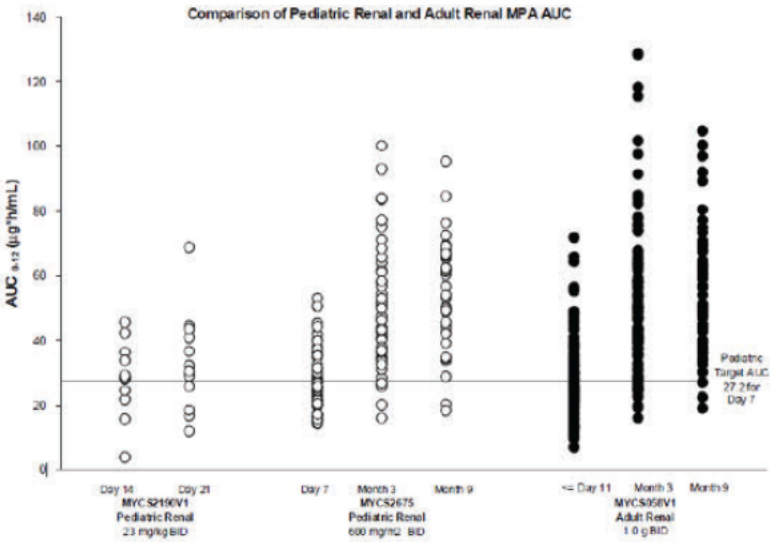
Figure 3. Dose-adjusted MPA AUC0-12 versus continuous age in the early post-transplant period (Day 7) in pediatric kidney transplant recipients using data from Study MYCS 2675.



(*Source: Expert Report P-180603, page 56, module 5.3.3.2, NDA 50722/S-049, SDN 1050, submitted Sept. 10, 2021*)

Overall, MPA PK in pediatric kidney transplant recipients is similar to that in adult kidney transplant recipients. Across both pediatric PK studies (MYC 2190 and MYCS 2675), MPA AUC_{0-12} at doses of 23 mg/kg BID or 600 mg/m^2 BID is similar to that in adult kidney transplant recipients at a dose of 1 g BID (**Figure 4**). Non-stationarity in PK is also consistently observed between pediatric and adult patients with increases in MPA AUC_{0-12} observed in the late vs. early post-transplant period. Similarity in AUC is further supported by the pediatric (study MYCS 2675) vs. adult (Study MYC 058) MPA AUC mean ratio [95% CI], which were 102 [89, 115]% and 107 [94, 122]% for untransformed and log-transformed data, respectively.

Figure 4. Comparison of MPA AUC0-12 in studies of pediatric (MYC 2190 and MYCS 2675) and adult (MYC 058) kidney transplant recipients.

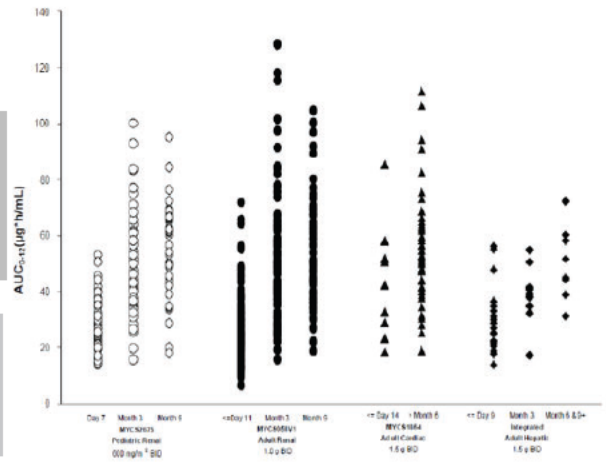


AUC=area under the plasma concentration-time curve; $AUC_{0\text{-}12h}$=area under the plasma concentration-time curve from time 0 h to time 12 h; BID=twice daily; MPA=mycophenolic acid.

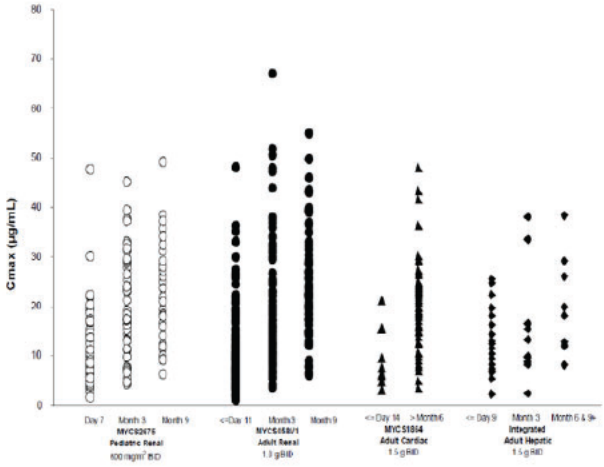
(*Source: Summary of Clinical Pharmacology, page 37, module 2.7.2, NDA 50722/S-049, SDN 1050, submitted Sept. 10, 2021*)

Lastly, MPA PK is similar between pediatric kidney transplant recipients and all adult transplant indications at their respective approved doses, with overlap observed for both $AUC_{0\text{-}12}$ and C_{max} (**Figure 5**).

Figure 5. Comparison of individual MPA AUC0-12 (left) and Cmax (right) across studies in pediatric kidney, and adult kidney, heart, and liver transplant patients.



$AUC_{0\text{-}12h}$=area under the concentration-time curve from Time 0 to 12 hours; b.i.d.=twice a day.
Source: Roche Report P-180594.



b.i.d.=twice a day; C_{max}=maximum concentration.
Source: Roche Report P-180594.

Note on the legend: Open circles – pediatric kidney transplant (600 mg/m^2 BID); black circles – adult kidney transplant (1 g BID); black triangles – adult heart transplant (1.5 g BID); black diamonds – adult liver transplant (1.5 g BID)

(*Source: Summary of Clinical Pharmacology, pages 79-80, module 2.7.2, NDA 50722/S-049, SDN 1050, submitted Sept. 10, 2021*)

PK in Pediatric Liver Transplant Recipients

The Applicant conducted Study PA 16497 to determine the safety, tolerability and PK of MMF in pediatric liver transplant recipients concomitantly treated with cyclosporine and corticosteroids. The study was originally designed in two parts: 1) an open-label, uncontrolled study to estimate the dose predicted to achieve an MPA AUC_{0-12} of 58 mcg*h/mL, and 2) an open-label, single-arm confirmatory PK study of the dose determined in part 1. Due to recruitment difficulties and infrequent use of triple immunosuppressive therapy including MMF, cyclosporine, and corticosteroids, the study was terminated early and only part 1 of the study was completed. For additional details regarding study design, patient demographics, PK analysis, and data adjustments, refer to Section 19.4.

The rationale for the desired AUC of 58 mcg*h/mL is derived from the average MPA AUC_{0-12} of 29.2 mcg*h/mL achieved in adult liver transplant patients in the early post-transplant period (value derived from the current approved CellCept label available at Drugs FDA, Roche 2021). Under the assumption that MPA AUC approximately doubles in the late post-transplant period relative to the early post-transplant period (non-stationarity in MPA PK), the target AUC in pediatric liver transplant patients in the late post-transplant period was set at 58 mcg*h/mL.

The study enrolled 9 pediatric patients aged 9 to 60 months who received a first liver allograft from a cadaveric or living donor and were at least 6 months post-transplant and therefore considered to be in the late post-transplant period. Subjects were dosed per center practice and received doses ranging from 200 to 424 mg/m^2. Thus, relative to the approved dosage in pediatric kidney transplant recipients, subjects in Study PA 16497 were underdosed. The Applicant's rationale for this is that, per center practice, the dose administered was determined by subject BSA at transplant and was not adjusted to increasing BSA over time. Since most subjects received their transplant between 1 and 2 years of age, it is possible that body weight would have increased significantly between the time of transplant and the time of study enrollment.

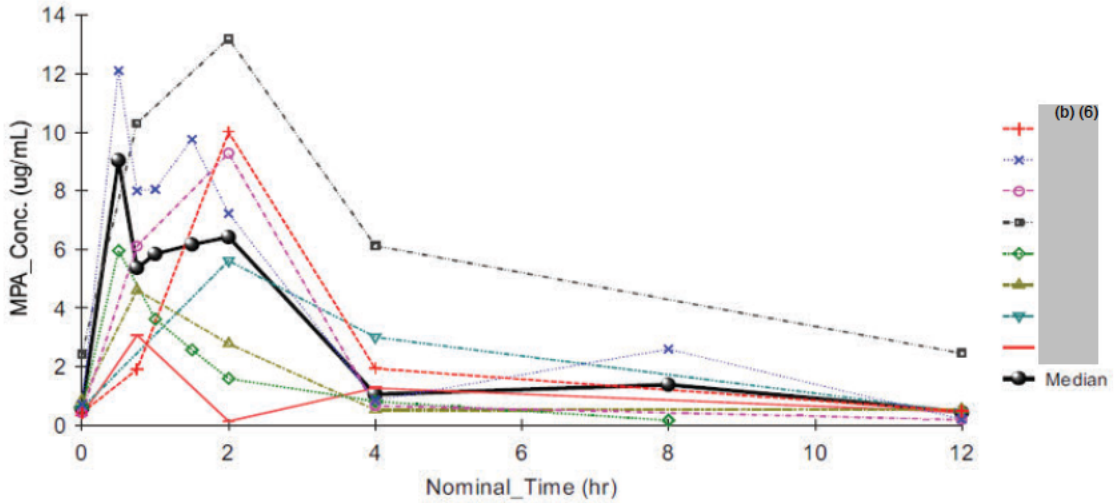
PK was evaluated in 8 out of 9 subjects. PK sampling was dependent on age with additional samples collected in subjects at least 24 months of age. In subjects younger than 24 months of age (n = 6), PK samples were collected pre-dose, and post-dose at hours 0.75, 2, 4, and 12. In subjects 24 months of age and older (n = 2), PK samples were collected pre-dose, and post-dose at hours 0.5, 0.75, 1, 1.5, 2, 4, 8, and 12.

Individual raw MPA plasma concentration vs. nominal time profiles are shown in **Figure 6**. Raw and dose normalized MPA PK parameters are shown in **Table 10**. As observed in adult populations and in pediatric kidney transplant recipients, high inter-individual variability in MPA PK was observed. The median concentration-time profile is represented by the black solid line in **Figure 6**. Subject (b) (6) represented by the black dashed line in **Figure 6**, was excluded as

an outlier from the MPA PK summary analyses shown in **Table 10** as this subject achieved a raw AUC more than two-fold higher than other subjects (raw MPA AUC_{0-12} for subject (b) (6) = 73.2 mcg*h/mL vs. geometric mean raw MPA AUC_{0-12} for remaining subjects = 20.4 mcg*h/mL).

Typical MPA plasma concentration vs. time profiles show a second peak within the 6 to 12 hour range as a result of enterohepatic recirculation in which MPAG is secreted in bile, converted to MPA, and re-absorbed. It is suggested that no second MPA peak is observed in liver transplant recipients as these patients lack a gallbladder and are therefore continuously excreting bile into the small intestine, rendering biliary MPAG continuously available for enterohepatic recirculation. In Study PA 16497, 6 out of 8 patients were younger than 24 months of age and therefore did not have PK samples collected between 6 and 12 hours post-dose. In the remaining two subjects, one sample was collected 8 hours post-dose. MPA concentrations appear to increase at 8 hours in one of these subjects (subject (b) (6) represented by the blue Xs in **Figure 6**), but decrease in the other subject (subject (b) (6) represented by the green diamonds in **Figure 6**). Due to the low sample size, it is difficult to make any definitive conclusions regarding MPA disposition in pediatric liver transplant recipients.

Figure 6. Raw MPA plasma concentrations vs. nominal time in pediatric liver transplant recipients in Study PA 16497.



(*Source: Clinical Study Report for Study PA 16497, page 28, module 5.3.3.2, NDA 50722/S-049, SDN 1050, submitted Sept. 10, 2021*)

Table 10. Individual raw and dose-normalized (to 600 mg/m2 and 1.5 g) MPA PK parameters in pediatric liver transplant recipients in Study PA 16497. Patient (b) (6) is excluded as an outlier.

				Normalized to 600mg/m^2		Normalized to 1.5g	
Patient	T_{max} (h)	C_{max} (µg/mL)	AUC_{0-12h} (µg.h/mL)	C_{max} (µg/mL)	AUC_{0-12h} (µg.h/mL)	C_{max} (µg/mL)	AUC_{0-12h} (µg.h/mL)
(b) (6)	2.03	10.0	30.9	19.7	60.9	107	331
	0.50	12.1	37.2	17.1	52.7	72.6	223
	1.95	9.28	25.2	15.1	40.9	81.9	223
	0.52	5.96	11.0*	15.2	28.1*	71.5	132*
	0.63	4.61	14.0	8.85	26.8	55.3	167
	2.00	5.61	29.1	16.8	87.2	84.2	436
	0.75	3.07	11.5	8.66	32.5	46.1	173
Mean	1.20	7.23	22.7	14.5	47.0	74.1	241
SD	0.75	3.27	10.5	4.21	21.8	20.0	107
CV%	62.6	45.2	46.3	29.1	46.4	27.0	44.4
Median	0.75	5.96	25.2	15.2	40.9	72.6	223
Min	0.50	3.07	11.0	8.66	26.8	46.1	132
Max	2.03	12.1	37.2	19.7	87.2	107	436
Geometric Mean	1.00	6.58	20.4	13.9	43.2	71.7	223

Note: * = Patient 1005 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.

(*Source: Clinical Study Report for Study PA 16497, page 29, module 5.3.3.2, NDA 50722/S-049, SDN 1050, submitted Sept. 10, 2021*)

Excluding subject (b) (6) the geometric mean MPA AUC_{0-12} normalized to a dose of 600 mg/m^2 was 43.2 mcg*h/mL. It was therefore concluded that to achieve the target AUC of 58 mcg*h/mL in the late post-transplant period, a dose of 740 to 806 mg/m^2 would be required. A range is provided depending on whether the geometric or arithmetic mean is used: 43.2 or 47.0 mcg*h/mL, respectively. This lends support for the proposed dosing of 600 up to 900 mg/m^2 BID.

When normalized to the same dose, MPA AUC_{0-12} and C_{max} in pediatric liver transplant recipients is lower relative to those observed in pediatric kidney transplant recipients **(Table 11)**. This relationship between liver and kidney transplant recipients observed in pediatric patients is very similar to what has been observed in adults in which MPA AUC_{0-12} in liver transplant recipients is similar to that in adult kidney transplant recipients when the former receive a dose that is 50% greater. A comparison of MPAG PK parameters demonstrates higher MPAG exposure in pediatric liver vs. kidney transplant recipients. The rationale for this difference is unclear. Given that MPAG is not pharmacologically active, the clinical significance of this difference is also unclear.

Table 11. Comparison of MPA and MPAG (raw) AUC0-12 and Cmax normalized to a dose of 600 mg/m^2 from pediatric liver and kidney transplant patients in the late post-transplant period.

MPA	Liver (our study; n=7)	Kidney ([1]; n=12)
Mean ± SD $AUC_{0\text{-}12h}$ (µg.h/mL)	47.0 ± 21.8	60.9 ± 10.7
Mean ± SD C_{max} (µg/mL)	14.5 ± 4.21	30.4 ± 9.16
MPAG		
Mean ± SD $AUC_{0\text{-}12h}$ (µg.h/mL)	[(a)]924 ± 341	453 ± 132
Mean ± SD C_{max} (µg/mL)	110 ± 45.6	64.8 ± 17.6

Note: (a) n=6 since MPAG $AUC_{0\text{-}12h}$ was not calculable for Patient 2002

(*Source: Clinical Study Report for Study PA 16497, page 34, module 5.3.3.2, NDA 50722/S-049, SDN 1050, submitted Sept. 10, 2021*)

Per the approved labeling for CellCept, the mean ± SD MPA $AUC_{0\text{-}12}$ and C_{max} in adult liver transplant patients > 6 months post-transplant receiving 1.5 g BID (n = 6) were 49.3 ± 14.8 mcg*h/mL and 19.3 ± 11.7 mcg/mL, respectively. In the late post-transplant period, the MPA exposure achieved in pediatric liver transplant patients when normalized to a dose of 600 mg/m^2 is approximately equal to the MPA exposure achieved in adult liver transplant patients receiving 1.5 g BID.

MPAG $AUC_{0\text{-}12}$ when normalized to a dose of 600 mg/m^2 and adjusted based on molecular weight to MPA equivalents in pediatric liver transplant recipients appears lower relative to the equivalent value in adult liver transplant recipients. The mean ± SD MPAG $AUC_{0\text{-}12}$ in the late post-transplant period for pediatric and adult liver patients were 548 ± 202 and 940 ± 379 mcg*h/mL, respectively (pediatric value derived from the Clinical Study Report for Study PA 16497, page 55, module 5.3.3.2, NDA 50722/S-049, SDN 1050, submitted Sept. 10, 2021; adult value derived from the original Biopharmaceutics Review for NDA 50722/S-005). Note that the value specified for pediatric liver transplant patients differs from that provided in **Table 11**, which was not adjusted for molecular weight.

A similar relationship in MPAG PK between pediatric and adult patients was also observed for kidney transplant recipients in which statistically significant differences were observed across all age groups with exposure increasing from the youngest to oldest patients (Study MYCS 2675). It was also indicated that the MPAG exposure in all pediatric patients was lower than that observed in adults. The Applicant has hypothesized that differences in MPAG exposure may be partly explained by a reduced capacity for renal tubular elimination of MPAG in older patients. MPAG AUC correlated positively with serum creatinine, and negatively with creatinine clearance suggesting that MPAG accumulates in patients with renal impairment (*Source: Expert Report P-180603, module 5.3.3.2, NDA 50722/S-049, SDN 1050, submitted Sept. 10, 2021*). It is also noteworthy that the majority of pediatric liver transplant patients from which MPAG PK information was determined were younger than 24 months of age, further emphasizing this relationship observed in pediatric vs. adult liver transplant recipients. Thus, when considering

MPAG PK behavior in pediatric vs. adult patients, further similarity exists among liver and kidney transplant recipients.

PK in Pediatric Heart Transplant Recipients

The Applicant provided two sources from the published literature to summarize the clinical pharmacology experience in pediatric heart transplant recipients. The Applicant has not conducted any clinical studies in this population.

- Dipchand AI, Pietra B, McCrindle BW, et al. Mycophenolic acid levels in pediatric heart transplant recipients receiving mycophenolate mofetil. *J Heart Lung Transplant*. 2001;20(10):1035-43.
- Gajarksi RJ, Crowley DC, Zamberlan MC, Lake KD. Lack of correlation between MMF dose and MPA level in pediatric and young adult cardiac transplant patients: Does the MPA level matter? *Am J Transplant.* 2004;4(9):1495-1500.

Both studies are retrospective analyses of data regarding the use of MMF in pediatric heart transplant recipients. The study by Dipchand *et al*. looked at data from the pediatric heart transplant database between November 1997 and October 1998. The study by Gajarski *et al*. looked at data generated between November 2001 and September 2003. Neither of these studies was conducted by the Applicant. However, given the years of publication and dates of observation, it is very likely that the form of MMF given to patients was CellCept, the Applicant's formulation. Per information available in FDA's Orange Book, the earliest available time at which generic MMF formulations became available was in 2008.

Dipchand AI, Pietra B, McCrindle BW, et al. Mycophenolic acid levels in pediatric heart transplant recipients receiving mycophenolate mofetil. *J Heart Lung Transplant*. 2001;20(10):1035-43

Table 12. Study design details and population information from the publication by Dipchand et al. J Heart Lung Transplant. 2001;20(10):1035-43.

INDICATION	Pediatric Heart Transplant
TITLE, AUTHORS, REFERENCE OF PUBLICATION	Dipchand et al.: Mycophenolic acid levels in pediatric heart transplant recipients receiving mycophenolate mofetil. J Heart Lung Transplant 20(10), 1035-1043, 2001.
OBJECTIVES	Review experience with mycophenolate mofetil (MMF) dosing and the role of mycophenolic acid (MPA) levels for therapeutic drug monitoring in a population of pediatric heart transplant patients.
STUDY DESIGN	Retrospective analysis of data obtained from the pediatric heart transplant database between November 1, 1997 and October 15, 1998. The data included all serum trough MPA levels, patient age, height, indication for and dose of MMF, other medications and details of all episodes of graft rejection. MMF was given concomitantly with cyclosporine A (CsA) or tacrolimus (TAC).
NUMBER OF SUBJECTS	44 patients (17 females, 27 males); total of 128 serum trough MPA levels measured by enzyme multiplied immunoassay technique (EMIT) assay.
DEMOGRAPHIC DATA	Median age at transplant 2.7 years (7 days to 18.4 years).

(*Source: Summary of Clinical Pharmacology, page 41, Module 2.7.2, NDA 50722/S-049, SDN 1050, submitted Sept. 10, 2021*)

For all patients, the median [range] age at transplant was 2.7 years (7 days to 18.4 years) and at the time of review, was 6.3 years (29 days to 23.5 years). MMF treatment was used for induction in 18 patients, induction and rejection in 23 patients, and graft vasculopathy in 3 patients. Note that in this study, therapeutic levels were defined as achieving an MPA trough > 3 µg/mL. Also note, that the paper itself reports values in units of ng/mL. The Applicant has assumed that they meant µg/mL. It has also been indicated that the MMF used was the product supplied for Roche. For infants and younger children, the dose was crushed into a powder and administered orally with water.

Table 13 below determines the dose required to achieve the therapeutic level of MPA trough > 3 µg/mL. The determinations were based on mixed linear regression modeling that looked at the relationships between MPA levels, dose, age, and interval from transplantation. Doses are reported in mg/kg and in mg/m^2 and trends appear similar when comparing doses at each level. Based on **Table 13,** higher doses are required in younger patients < 5 years of age. Dosing appears comparable in children aged 5 to > 16 years. Although it is not explicitly stated, it appears that the dose reported is daily dose (as opposed to BID dose).

Table 13. MMF dose needed to achieve MPA trough levels > 3 mcg/mL 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/m²	2,189±696	2,254±887	1,833±931	1,573±833	1,792±579

MPA=mycophenolic acid.
* Therapeutic level: >3 µg/mL.
** Number of patients in that age range on the date of MPA level.

(*Source: Summary of Clinical Pharmacology, page 42, Module 2.7.2, NDA 50722/S-049, SDN 1050, submitted Sept. 10, 2021*)

When looking at the relationship between MPA dose and time post-transplant, non-stationarity of dosing is supported **(Table 14**). Up to 8 weeks post-transplant, the average dose received by all patients steadily increased. It is hypothesized that this may have been due to upward titration to increase MPA levels above sub-therapeutic. However, the dose required to achieve an MPA trough > 3 mcg/mL was decreased > 8 weeks post-transplant.

Table 14. MMF dose needed to achieve MPA trough levels > 3 mcg/mL by time post-transplant.

	Time post-transplant					
	<1 week	1 to 2 weeks	2 to 4 weeks	4 to 6 weeks	6 to 8 weeks	>8 weeks
# of patients	5	13	11	10	8	28
# of levels	5	15	13	15	8	71
# of patients with therapeutic levels*	0	1	1	1	6	16
# of therapeutic levels*	0	1	1	2	6	28
Dose						
mg/kg (all patients)	54±24	69±23	86±18	93±31	111±21	60±30
mg/m^2 (all patients)	1,352±392	1,449±422	1,830±427	2,076±829	2,433±555	1,584±633
mg/kg (therapeutic*)	—	110	68	109±9	109±24	59±34
mg/m^2 (therapeutic*)	—	1,766	2,411	2,932±243	2,601±542	1,711±682

MPA=mycophenolic acid.
*Therapeutic level >3 µg/mL.

(*Source: Summary of Clinical Pharmacology, page 43, Module 2.7.2, NDA 50722/S-049, SDN 1050, submitted Sept. 10, 2021*)

Table 15 below shows the incidence of rejection episodes based on MPA levels in 33 patients that received MMF induction for the first 8-weeks post-transplant. Among 10 patients with therapeutic levels, 4 experienced no rejection episodes. Among 10 patients without therapeutic levels, 6 experienced no rejection episodes. For the remaining 13 patients, MPA levels were not measured within the 8-week timeframe.

Table 15. Number of rejection episodes based on MPA trough levels in the first 8 weeks post-transplant.

	# of rejection episodes	No rejection
Therapeutic level*	7 (6 patients)	4
No therapeutic level*	5 (4 patients)	6
Level not checked in first 8 weeks	23 (13 patients)	—
Total	35 in 23 patients = 1.5 episodes/patient	

*Level >3.0 ng/ml.

(*Source: Table VI, Dipchand* et al. J Heart Lung Transplant*. 2001;20(10):1035-43*)

There are numerous caveats that would preclude use of specific quantitative information from the paper by Dipchand *et al*. This study was not prospectively designed and subject-level data

has not been provided. This paper also reports that in some cases MMF was given to treat rejection instead of for prevention of rejection. Patients experiencing rejection episodes may differ from those that did not experience rejection episodes in clinically important ways, including possible differences in MPA levels. Thus, the applicability of this data is questionable to support approval for prevention of rejection in pediatric heart transplant recipients. Lastly, the information derived is based on achieving MPA trough concentrations at a therapeutic level > 3 mcg/mL. Due to wide variability in MPA PK and data provided by the authors (**Table 14**), it is not clear that an MPA therapeutic level of 3 mcg/mL adequately predicts efficacy.

Despite these caveats, there are a number of qualitative observations derived from this paper that support PK similarity between pediatric heart transplant recipients and other transplant populations. The authors concluded that higher MMF doses may be needed in younger patients. This observation matches what was previously observed by the Applicant in pediatric kidney transplant recipients in which patients younger than 2 years of age had numerically lower MPA AUC_{0-12} relative to older age groups (Study MYCS 2675). In addition, the authors of this study concluded that higher MMF doses may be needed in the early post-transplant period relative to the late post-transplant period to achieve therapeutic levels (non-stationarity in MPA PK). Lastly, MMF was given in this study either concomitantly with cyclosporine or tacrolimus. The authors also concluded that lower MMF doses may be needed when administered concomitantly with tacrolimus. This phenomenon is also observed in other transplant populations in which cyclosporine is known to interfere with enterohepatic recirculation and overall decrease MPA exposure.

Gajarksi RJ, Crowley DC, Zamberlan MC, Lake KD. Lack of correlation between MMF dose and MPA level in pediatric and young adult cardiac transplant patients: Does the MPA level matter? *Am J Transplant* 2004;4(9):1495-1500.

Table 16. Study design details and population information from the publication by Gajarski et al. Am J Transplant 2004;4(9):1495-1500.

INDICATION	Pediatric Heart Transplant
TITLE, AUTHORS, REFERENCE OF PUBLICATION	Gajarski RJ et al.: Lack of correlation between MMF dose and MPA level in pediatric and young adult cardiac transplant patients: Does the MPA level matter? Am J Transplant 4(9), 1495-1500, 2004
OBJECTIVES	This study was designed to evaluate mycophenolate mofetil (MMF) dose-concentration correlations, to determine the frequency with which standard pediatric dosing achieved therapeutic plasma concentrations, and to determine if a 'threshold' mycophenolic acid (MPA) concentration exists which minimizes rejection risk.
STUDY DESIGN	Retrospective analysis of trough concentrations of MPA and its metabolite, mycophenolic acid glucuronide (MPAG), measured following MMF doses of 1200 mg/m^2/day (max 3000 mg/day) together with corresponding endomyocardial biopsy (EMB) grades and calcineurin inhibitor levels. MMF was given concomitantly with cyclosporine A (CsA) or tacrolimus (TAC). Observation time span November 2001 to September 2003.
NUMBER OF SUBJECTS	26 patients (16 children, 10 adults); total of 120 MPA and MPAG trough levels measured by an high performance liquid chromatography (HPLC) assay.
DEMOGRAPHIC DATA	Mean±SD age 15.4±9.5 years, 1 month - 33 years

(*Source: Summary of Clinical Pharmacology, page 44, Module 2.7.2, NDA 50722/S-049, SDN 1050, submitted Sept. 10, 2021*)

This study was a retrospective analysis of medical records from pediatric and young adult heart transplant recipients who received MMF immunosuppression. Between Nov. 2001 and Sept. 2003, 26 patients, including 16 children and 10 adults (age 15.4 ± 9.5 years; range: 1 month to 33 years) had 120 MPA and MPAG concentrations measured, with 50% obtained during the first-year post-transplant. The average MMF daily dose was 37.9 ± 12.5 mg/kg and 1206.8 ± 301.9 mg/m^2. Using this standard dosing, only 50% of patients consistently achieved lower-limit therapeutic MPA trough levels, defined by the study as > 1.0 µg/mL. Wide fluctuations in intra-individual MPA concentrations were identified. In addition, no association was determined between MMF dose (either in mg/kg or in mg/m^2) and serum MPA or MPAG concentrations.

Among the 16 pediatric patients, 8 concomitantly received cyclosporine A, while the other 8 received tacrolimus. MPA trough concentrations were higher in children receiving tacrolimus (3.0 ± 2.2 vs. 1.6 ± 1.5; p = 0.04). For children and adults on cyclosporine A (8 children and 10 adults), there was no difference in MMF dosing (1279.9 ± 359.3 mg/m^2/day vs. 1174.6 ± 269.2 mg/m^2/day). Children trended toward lower MPA trough concentrations, but this was not significant (1.6 ± 1.5 µg/mL vs. 2.3 ± 2.2 µg/mL; p = 0.06). MPAG levels were higher in adults compared to children (98 ± 47 µg/mL vs. 48 ± 37 µg/mL). Renal impairment did not contribute to this finding as it was similar between adults and children. It was suggested that this finding may be due to age and possibly due to the effects of the calcineurin inhibitor used. The latter point could not be examined as there were no adults who received tacrolimus. MPAG/MPA

ratios were significantly higher for children receiving cyclosporine A relative to those receiving tacrolimus. However, among adults and children receiving cyclosporine A, the MPAG/MPA ratio was higher for adults relative to children.

When evaluating endomyocardial biopsy scores obtained with concurrent MPA/MPAG levels, there was a non-statistically significant trend toward lower MPA levels among patients with biopsy grade 2 or higher compared with those with lower-grade biopsies. Note that higher grade biopsies are associated with rejection episodes. Biopsy grades ≥ 2 were associated with significantly lower MPA concentrations (1.05 ± 1.0 μg/mL) compared with lower grade biopsies (2.3 ± 2.4 μg/mL).

Similar to the publication by Dipchand *et al*., there are some limitations to the available data in this study. Much like the study conducted by Dipchand *et al*., MPA PK information is reported based on MPA trough levels, which have not been established for efficacy. It is therefore difficult to use this information to compare PK information with available data in other transplant populations. In addition, this study evaluated both pediatric patients and young adults. Although the mean age and overall age range have been provided (15.4 years and 1 month to 33 years, respectively), subject level data has not been provided. The age distribution of pediatric patients is therefore unclear.

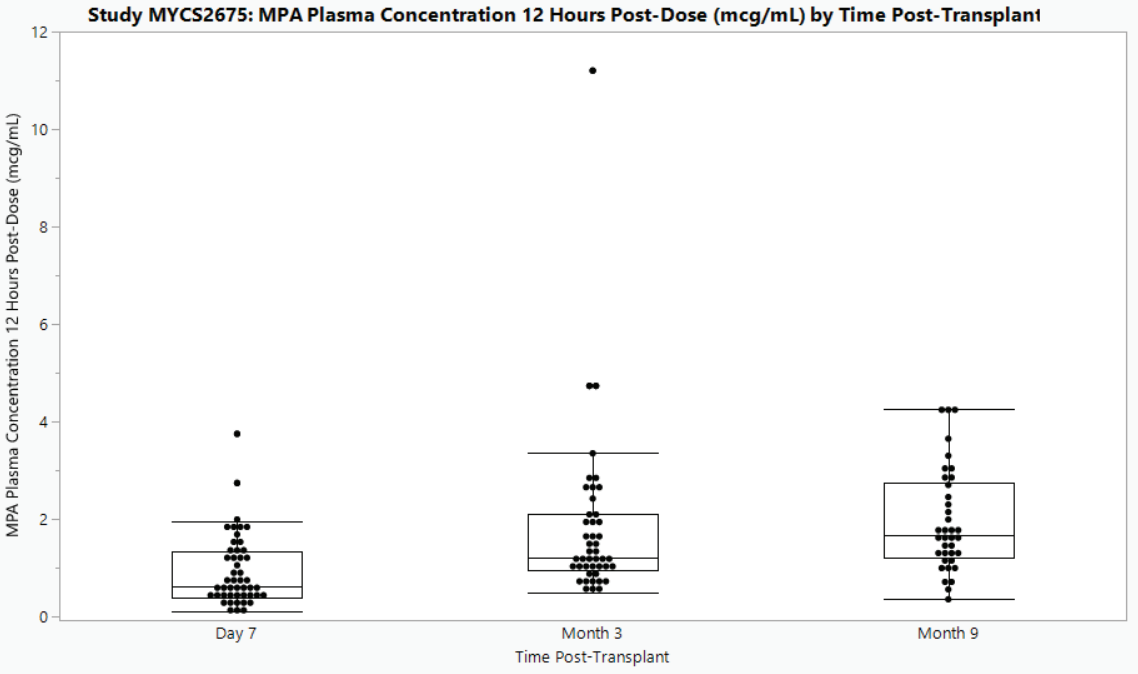
Despite the limitations, there are several qualitative observations that support PK similarity between pediatric heart transplant recipients and other approved transplant populations. For example, higher MPA concentrations were observed in pediatric patients taking concomitant tacrolimus relative to those concomitantly taking cyclosporine, which has been observed across transplant populations. In this study, MPAG trough levels in adults were determined to be higher than that in pediatric patients among those concomitantly taking cyclosporine. This relationship in MPAG PK between adults vs. pediatric patients has also been observed among kidney transplant and liver transplant recipients as described earlier in this review.

Among pediatric and young adult pediatric heart transplant recipients receiving the same dose of MMF and concomitantly taking cyclosporine, it was determined that MPA trough concentrations in pediatric patients were numerically, but not significantly, lower than those measured in adult patients. This suggests that MPA PK behavior may be similar in pediatric and adult heart transplant patients.

Because MPA PK information in the study by Gajarski *et al*. was provided in terms of MPA trough concentrations, it is difficult to make comparisons with available PK data in other transplant populations, which are primarily described based on MPA $AUC_{0\text{-}12}$. To facilitate a comparison of PK with pediatric kidney transplant recipients, average MPA trough concentrations were calculated using data from Study MYCS 2675 and compared to values reported by Gajarski *et al*. Average trough concentrations in Study MYCS 2675 were calculated using the MPA plasma concentrations at 12 hours post-dose (**Figure 7**). Values were averaged based on the time post-transplant (Day 7, Month 3, and Month 9). Similar to what is observed

when exposure is summarized based on AUC, high inter-individual variability in MPA trough concentrations was observed across all time points. Non-stationarity in MPA PK is also apparent, with increases in the average trough concentration observed in the late vs. early post-transplant period.

Figure 7. MPA plasma concentrations 12-hours post-dose by time post-transplant in pediatric kidney transplant recipients from Study MYCS 2675.



(*Source: Reviewer-generated plot using data provided in the study report for Study MYCS 2675, Module 5.3.3.2, NDA 50722/S-049, SDN 1050, submitted Sept. 10, 2021*)

The mean ± SD [range] MPA trough concentrations in pediatric kidney transplant recipients at Day 7, Month 3, and Month 9 post-transplant were 0.87 ± 0.74 [0.10, 3.74] mcg/mL, 1.79 ± 1.74 [0.48, 11.2] mcg/mL, and 1.92 ± 1.06 [0.34, 4.26] mcg/mL, respectively. Based on the study conducted by Gajarski *et al*., among pediatric heart transplant patient recipients receiving similar daily doses of MMF as in MYCS 2675 (1279.9 ± 359.3 mg/m^2/day ≈ 600 mg/m^2 BID) and concomitantly taking cyclosporine, the average MPA trough concentration was 1.6 ± 1.5 mcg/mL. Thus, the observed MPA trough concentrations in the late post-transplant period in pediatric kidney transplant recipients matches the reported concentrations in pediatric heart transplant recipients and suggests that MPA PK is similar across both populations.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Effectiveness in pediatric liver and heart transplant recipients is based on extrapolation from pediatric kidney, and adult kidney, liver, and heart transplant recipients. The Applicant did not submit any new clinical pharmacology studies that would provide supportive evidence of effectiveness. Study PA 16497 was an uncontrolled, open-label study designed to estimate the MMF dose predicted to achieve an exposure of 58 mcg*h/mL in pediatric liver transplant recipients in the late post-transplant period. Due to the study design, no evidence of effectiveness can be inferred.

Per the original clinical pharmacology review for CellCept in pediatric kidney transplant recipients (NDA 50722/S-007), it was noted that the premise for development in the pediatric population was based on similarity between adults and pediatric patients in the course of acute rejection, the MMF mechanism of action, and MMF metabolism. As a result, extrapolation of efficacy from adults to pediatric patients was deemed appropriate. As observed in the pediatric kidney transplant program, a dose derived using adult data provided MPA AUC values in the pediatric population associated with the recommended adult dose. It is purported that the mechanism of acute rejection of solid organ allografts are independent of the specific organ type. Of note, this argument was also used to support approval of CellCept in adult liver transplant recipients (NDA 50722/S-005). Thus, it appears appropriate that extrapolation of efficacy may also be applied to pediatric heart transplant and liver transplant recipients.

Based on the PK data described above, including established PK relationships between approved transplant populations, the following are inferred:

- Similar PK between pediatric and adult kidney transplant populations
- Similar PK between pediatric and adult liver transplant populations
- PK relationships between pediatric kidney transplant and liver transplant patients that mimic what is observed in the adult populations
- Similar PK between pediatric kidney and heart transplant populations with higher dosing needs in pediatric heart transplant patients to prevent loss of the graft.

Therefore, extrapolation of efficacy at the proposed doses for pediatric heart transplant and liver transplant recipients is reasonable from a clinical pharmacology perspective.

<u>Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?</u>

Summary
The proposed oral MMF dosing regimen of 600 mg/m^2 up to a maximum of 900 mg/m^2 appears appropriate for the prevention of organ rejection in pediatric heart transplant and liver transplant patients 2 years of age and older. Due to limited available data in patients younger than 2 years of age, it is not clear whether the proposed doses will be appropriate in this age group. The recommended dosage of 600 mg/m^2 BID is approved in pediatric kidney transplant patients down to 3 months of age and supports the application of this dosage in this age group in other transplant populations. However, information from the literature suggests that

patients younger than 2 years of age may exhibit important differences with impacts to MPA disposition. The Applicant has proposed [redacted] We therefore do not find the proposed [redacted] acceptable.

Recommended Dosage in Adult Transplant Populations
The recommended oral MMF dosage in adult kidney transplant patients for the prevention of organ rejection is 1 g BID. The evidence for this dosing regimen was derived from two pivotal, blinded, azathioprine-controlled studies. The recommended oral MMF dosage in adult heart transplant and liver transplant patients for the prevention of organ rejection is 1.5 g BID.

MPA PK following MMF dosing in heart transplant patients has been shown to be similar to that in kidney transplant patients. The rationale for increasing the MMF dosage in heart transplant patients relative to kidney transplant patients is to prevent loss of the graft. This is especially given the lack of alternative treatments in the case of failure of the heart graft as well as the limited availability of donor hearts. The selection of the 3 g/day (1.5 g BID) dose was based on a risk-benefit assessment in which the consequences of graft rejection justified the selection of a higher dose and potential associated increase in adverse events. Per the original Medical Officer's review for MMF in heart transplant patients (NDA 50722/S-002), it was concluded that the 3 g/day (1.5 g BID) dosing regimen was at least as effective for the prevention of cardiac allograft rejection as established azathioprine-based regimens.

MPA PK after MMF dosing in liver transplant patients is lower than that in kidney transplant patients at the same dose. As a result, liver transplant patients have higher dosing needs to achieve similar MPA exposure to that in kidney transplant patients. The lower exposure provides the rationale for increasing the MMF dosage in liver transplant patients. Per the original review for MMF in liver transplant patients (NDA 50722/S-005), the chosen dosage of 1.5 g BID was based on PK information suggesting that this dose would produce MPA plasma concentrations similar to those produced in kidney transplant patients receiving a dosage of 1 g BID.

Recommended Dosage in Pediatric Transplant Populations
In pediatric kidney transplant patients 3 months of age and older, the recommended oral dosage of 600 mg/m^2 BID was derived based on achieving the same MPA AUC_{0-12} as that in adults following the 1 g BID regimen. The successful application of MPA exposure values for the derivation of an appropriate dose in the pediatric population suggests that extrapolation is a viable approach.

The available clinical pharmacology data, described in previous sections, has provided evidence suggesting that PK relationships across pediatric transplant populations mimics those observed across adult transplant populations. This includes similarity in PK between kidney transplant and heart transplant patients, and lower exposure at the same dose in liver transplant patients relative to kidney transplant patients. The proposed minimum dosage of 600 mg/m^2 BID has precedence as the recommended dosage in kidney transplant patients. The proposed maximum dosage of 900 mg/m^2 BID represents a 50% increase over the minimum dosage and arithmetically matches the increase in the dosage recommended for adult heart transplant and liver transplant patients. Given the high inter-individual variability in MPA exposure after MMF dosing and the potential for increased adverse events at the highest dose, proposing a range between 600 and 900 mg/m^2 appears appropriate from a clinical pharmacology perspective.

Uncertainty in Patients Younger than 2 Years of Age
Although the proposed dosing regimen of 600 up to 900 mg/m^2 BID generally appears appropriate from a clinical pharmacology perspective, there is some uncertainty regarding whether MPA exposure in patients younger than 2 years of age will match that observed in older pediatric patients. The reason for this uncertainty is due to ontogenetic differences in expression of enzymes important for MPA activity and disposition.

MPA activity is independent of the specific organ type as its primary mechanism of action is through the inhibition of IMPDH which produces cytostatic effects on B and T lymphocytes. It is suggested that IMPDH does not undergo ontogenetic changes in children 2 years of age and older. In a study conducted by Rother *et al*., IMPDH activity in peripheral blood mononuclear cells (PBMCs) was analyzed in 79 healthy children aged 2 to 17.9 years and compared with that from 106 healthy adults[4]. Results from this study determined that there was no developmental regulation of IMPDH as median IMPDH activity did not differ across age groups. Children under 2 years of age were not evaluated in this study, and no additional information has been provided to describe IMPDH expression and activity in this age group. It is therefore unclear whether there may be ontogenetic differences in IMPDH in children younger than 2 years of age that would impact MPA activity in this age group.

MPA plasma concentrations are dependent on metabolism via glucuronidation in the liver to MPAG, which leads to enterohepatic recirculation following MPAG secretion in bile and glucuronide cleavage. Based on literature sources provided by the Applicant, the activity of uridine diphosphate glucuronosyltransferase (UGT) enzymes is deficient at birth and absent from the fetal liver, but increases to reach adult levels by approximately 2 to 4 years of age[5,6]. This is consistent with observations in pediatric kidney transplant patients in which MPAG

[4] Rother A, Glander P, Vitt E, *et al.* Inosine monophosphate dehydrogenase activity in paediatrics: age-related regulation and response to mycophenolic acid. *Eur J Clin Pharmacol*. 2012;68(6):913-922.
[5] Anderson GD. Developmental pharmacokinetics. *Semin Pediatr Neurol*. 2010;17(4):208-13.
[6] Miyagi SJ, Collier AC. Pediatric development of glucuronidation: the ontogeny of hepatic UGT1A4. *Drug Metab Dispos*. 2007;35(9):1587-92.

exposure increased from the youngest to the oldest patients. Although, this may have also been driven by age-related differences in renal elimination. It is unclear how and to what extent deficient UGT activity may contribute to differences in MPA exposure in children younger than 2 years of age. Per the approved labeling for CellCept, MPA AUC increased by approximately 35% when MMF was concomitantly administered with isavuconazole, a UGT inhibitor. However, there are other myriad age-related factors that, in tandem, affect MPA disposition and exposure.

Despite the potential differences in patients aged 3 months to 2 years of age, there is available data that suggests that MPA exposure may be similar in this age group as compared with older age groups. In Study MYCS 2675 in pediatric kidney transplant patients, MPA AUC_{0-12} in a subset of patients under 2 years of age was numerically, but not significantly, lower relative to older age groups. However, an examination of MPA AUC vs. age as a continuous variable did not suggest that there exists an age-related trend in exposure (**Figure 3**). Available data on safety, efficacy, and PK, supported the approval of the 600 mg/m^2 BID dosage in all pediatric patients down to 3 months of age. In addition, in Study PA 16497 in pediatric liver transplant patients, most patients (6/8) were under 2 years of age. Despite high inter-patient variability in MPA exposure, mean MPA AUC_{0-12} was approximately equal to that achieved in adult liver transplant patients receiving 1.5 g BID.

Overall, the available data in pediatric kidney transplant and liver transplant patients suggests that MPA exposure after MMF dosing remains approximately consistent across pediatric patients, including those younger than 2 years of age, and adults. However, high inter-individual variability in exposure has been observed with MMF dosing, and, in current clinical use, the dose may be modified based on factors such as tolerability and concomitant medications.

(b) (4)

In light of the uncertainty surrounding MPA exposure in pediatric patients younger than 2 years of age, the Applicant has not proposed a specific dosing regimen for this age group. The Applicant has instead proposed (b) (4)

(b) (4)

(b) (4)

(b) (4)

As a result, we do not agree with the Applicant's proposal (b) (4) Therefore, the proposed labeling for patients aged 3 months to < 2 years of age will permit flexibility in dosing at the clinician's discretion based on current use in clinical practice.

Safety of the Proposed Dosing Regimen
Some evidence of safety of the proposed dosing regimen can be derived from the clinical pharmacology program. Safety has been established in pediatric kidney transplant patients aged 3 months and older at a dose of 600 mg/m^2, which can be relied on to support safety in other pediatric transplant populations.

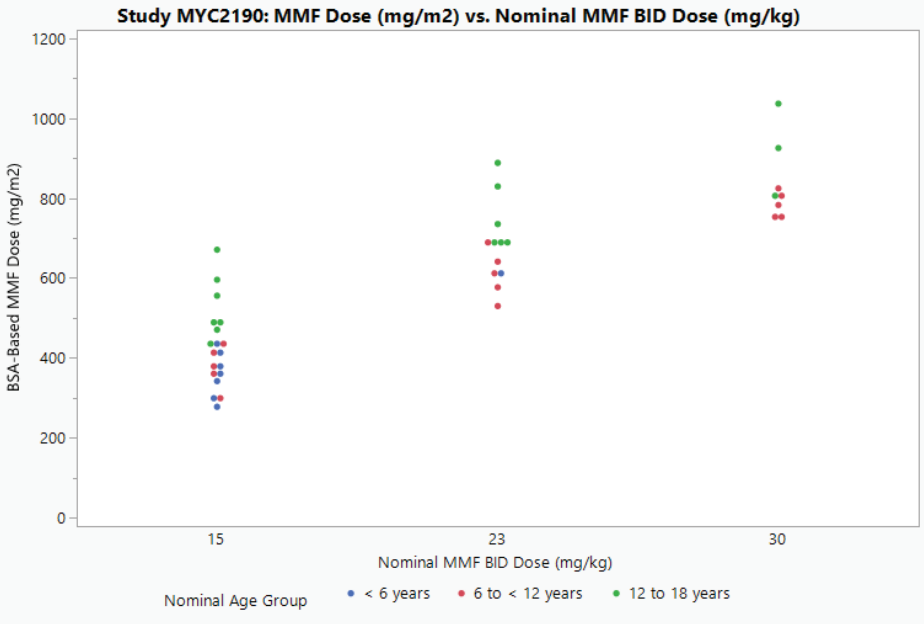
Based on MPA PK relationships across transplant populations described above, MPA exposure in pediatric liver transplant patients is approximately similar to that in pediatric kidney transplant patients when the former receives an MMF dose that is 50% greater. Thus, based on exposure matching, clinical pharmacology review has determined that safety of the proposed dosing regimen, up to the maximum dosage of 900 mg/m^2 BID (a dosage 50% greater than the recommended 600 mg/m^2 BID dosage in pediatric kidney transplant patients), is supported for pediatric liver transplant patients.

As described above, MPA exposure in pediatric heart transplant patients is approximately similar to that in pediatric kidney transplant patients at the same dose. Thus, based on exposure matching, clinical pharmacology evidence only supports the safety of the 600 mg/m^2 BID dosage in pediatric heart transplant patients.

Previous studies conducted by the Applicant in pediatric patients were reviewed to determine whether there had been any precedence for dosing MMF up to 900 mg/m^2 to potentially support the safety of this dose in pediatric heart transplant patients. Study MYC 2190 was conducted in pediatric kidney transplant patients as a dose-ranging pilot study to determine the MMF dose that would deliver an MPA $AUC_{0\text{-}12}$ of 27.2 mcg*h/mL (n = 40; age range: 1 to 18 years). This study was previously reviewed by the Agency to support approval of MMF for the prevention of organ rejection in pediatric recipients of kidney allografts (NDA 50722/S-007). At the time this study was conducted, it had not yet been determined that dosing based on BSA could reduce inter-subject variability in MPA exposure. Therefore, subjects were enrolled into one of three BID dose groups based on body weight: 15 mg/kg, 23 mg/kg, or 30 mg/kg. Data from this study suggested that those enrolled in the 23 mg/kg BID dose group most closely achieved the MPA AUC target of 27.2 mcg*h/mL. Based on linear regression analysis, 23 mg/kg was equated to a BSA-based dose of 600 mg/m^2, which was later confirmed in the pivotal pediatric Study MYCS 2675.

Subjects enrolled in the 30 mg/kg BID dose group therefore likely received doses greater than 600 mg/m^2. For all dose groups, BSA-based doses were derived from the weight-based doses using data provided in the MYC 2190 study report (**Figure 8**). This included the absolute MMF dose, calculated based on the actual dose received in mg/kg and subject weight, and individual subject height and weight. BSA was calculated using the Mosteller method, the same method used to calculate BSA in pivotal Study MYCS 2675.

Figure 8. Individual BSA-based MMF doses vs. nominal weight-based MMF doses stratified by age group in Study MYC 2190 in pediatric kidney transplant patients.



(*Source: Reviewer-generated plot using data provided in the study report for Study MYC 2190, Module 5.3.3.2, NDA 50722/S-049, SDN 1050, submitted Sept. 10, 2021*)

Figure 8 shows the distribution of BSA-based doses within each nominal weight-based dose group, with individual values stratified by age group. One subject who did not receive a dose equivalent to any of the three nominal doses was excluded. The plot in **Figure 8** shows generally increasing BSA-based doses with increasing nominal weight-based doses, although there is overlap across dose groups. Within each dose group, the highest BSA dose was given to the oldest children. The mean [range] BSA-based MMF dose corresponding to the 15 mg/kg, 23 mg/kg, and 30 mg/kg dose groups are 425.7 [277.8, 670.8] mg/m^2, 681.7 [529.9, 888.2] mg/m^2, and 834.4 [750.7, 1036.4] mg/m^2, respectively. This indicates that there is precedence for dosing pediatric patients with doses greater than approved, with subjects in all dose groups (including all subjects in the 30 mg/kg dose group) receiving dosages above the recommended 600 mg/m^2 dosage. Most subjects in the 30 mg/kg dose group received doses between 750 and 800 mg/m^2, although two subjects received doses above 900 mg/m^2, both in the oldest age group. One subject in the 23 mg/kg dose group received a BSA dose of 888 mg/m^2, close to the proposed maximum of 900 mg/m^2.

Study MYC 2190 provides precedence for dosing MMF in pediatric patients at dosages greater than the approved 600 mg/m^2 dosage. However, information at the proposed maximum dosage of 900 mg/m^2 is still limited, with only three pediatric patients aged 12 to 18 years receiving dosages at or above 900 mg/m^2. There is therefore limited clinical pharmacology evidence to support the safety of the proposed maximum dosage of 900 mg/m^2 in pediatric heart transplant patients.

Please refer to the clinical review in Section 8.2 for additional information regarding safety of the proposing dosing regimen.

<u>Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?</u>

Based on data submitted by the Applicant, this question is not applicable. No new data has been submitted to determine whether an alternative dosing regimen or management strategy is required for subpopulations based on intrinsic patient factors. The current approved labeling for CellCept describes the pharmacokinetics of MPA in the context of renal impairment, postoperative delayed renal graft function, hepatic impairment, and sex. For kidney transplant patients with severe chronic impairment of the graft (GFR < 25 mL/min/1.73 m^2), it is recommended not to administer doses greater than 1 g twice daily and to carefully monitor these patients. No other alternative regimens or management strategies are recommended based on intrinsic patient factors.

<u>Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?</u>

No new data has been provided regarding clinically relevant food-drug or drug-drug interactions. The current approved labeling for CellCept indicates that in the presence of food, there was no effect on MPA AUC. However, MPA C_{max} decreased by 40%. As a result, it is recommended that MMF be administered on an empty stomach, although it may be administered with food in stable transplant patients. The current CellCept labeling also describes information derived from several drug-drug interaction studies, including those with cyclosporine, proton pump inhibitors, and drugs affecting glucuronidation, etc.

Question on clinically relevant specifications (TBD)?

None.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

PK Study 16497 is the only new clinical study conducted in the proposed pediatric liver transplant population that was submitted in support of this application. Since this study is primarily a PK study, it is discussed in detail and reviewed in the Clinical Pharmacology section (Section 6) of this Unireview. Tabular information of studies conducted and reviewed as a part of prior applications for the approved indications are provided below.

Table 17. Listing of Clinical Trials Relevant to this NDA/BLA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Studies to support efficacy and safety in adult kidney transplant							
ICM 1866	Randomized (R), double-blind (DB), multi-center (MC), assessing safety and efficacy of MMF in combination with CsA and CS	Anti-thymocyte globulin (ATG) induction + MMF 1 gram (g) BID + CsA+CS (Arm 1) Or ATG induction + MMF 1.5 g BID + CsA + CS (Arm 2) Or Aza + CsA + CS (Arm 3)	Treatment failure within first 6 months of transplantation defined as: • BPAR or the occurrence of death/graft loss • Early termination for any reason without BPAR	12 months	Arm 1: N=167 Arm 2: N=166 Arm 3: N=166 (Total: N=499)	Adult kidney transplant	U.S./ Canada
MYC 023	R, DB, MC, assessing safety and efficacy of MMF in combination with CsA and CS	No induction MMF 1 g BID + CsA + CS (Arm 1) Or MMF 1.5 g BID + CsA + CS (Arm 2) Or AZA + CsA + CS (Arm 3)	Treatment failure within first 6 months of transplantation defined as: • BPAR or the occurrence of death/graft loss • Early termination for any reason without BPAR	12 months	Arm 1: N=173 Arm 2: N=164 Arm 3: N=166 (Total= 503)	Adult kidney Transplant	Europe / Canada / Australia
MYC 022	R, DB, MC, assessing safety and efficacy of MMF in combination	No induction MMF 1 g BID + CsA + CS (Arm 1) Or MMF 1.5 g BID + CsA + CS (Arm 2)	Treatment failure within first 6 months of transplantation defined as: • BPAR or the	12 months	Arm 1: N=165 Arm 2: N=160 Arm 3:	Adult kidney transplant	Europe

	with CsA and CS	Or Placebo + CsA + CS (Arm 3)	occurrence of death/graft loss • Early termination for any reason without BPAR		N=166 (Total= 491)		
Studies to support efficacy and safety in pediatric kidney transplant							
Trial Identity	**Trial Design**	**Regimen/ schedule/ route**	**Study Endpoints**	**Treatment Duration/ Follow Up**	**No. of patients enrolled**	**Study Population**	**No. of Centers and Countries**
MYC 2190	Open-label, dose-ranging, PK, safety, and tolerance study of oral MMF	15 mg/kg, 23 mg/kg or 30 mg/kg oral BID	• Assessment of PK and safety • Biopsy proven rejection at 6 months • Graft and patient survival at 1 and 3 years	3 years intended (terminated early)	N=40	Pediatric kidney transplant	U.S.
MYCS 2675	Open-label, single arm, PK, safety, tolerance, and efficacy study of MMF oral suspension	MMF oral suspension- 600 mg/ m^2 up to 1 g BID (as per local center practice) + CsA + CS	• Biopsy proven rejection at 6 and 12 months • Graft and Patient survival at 6 and 12 months	3 years	N=100	Pediatric kidney transplant	U.S./ Canada/ Europe/ Australia
Studies to support efficacy and safety in adult heart transplant							
MYCS 1864	R, DB, MC study assessing safety and efficacy of MMF versus azathioprine	MMF 1.5 g BID + CsA + CS (Arm 1) Or Aza (1.5-3 mg/kg/day) + CsA + CS (Arm 2)	• Biopsy proven rejection with hemodynamic compromise (6 months) • Death or Retransplantation (12 months)	3 years	Arm 1: N=289 Arm 2: N=289 N=578	Adult heart transplant	U.S./abroad (unable to identify, 28 centers)

Studies to support efficacy and safety in adult liver transplant							
MYCS 2646	R, DB, MC, study assessing safety and efficacy of MMF versus azathioprine	(Arm 1) MMF 1 g BID IV x 14 D, then MMF 1.5 g PO BID (Arm 2) AZA 1-2 mg/kg/day IV, then AZA 1-2 mg/kg/day PO + CsA + CS	• BPAR, and treated rejection • Death/ retransplantation	3 years	Arm 1: 278 Arm 2: 287 N=564	Adult liver transplant	U.S./Canada/ Europe/ Australia
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)-pediatric liver transplant							
Trial Identity	**Trial Design**	**Regimen/ schedule/ route**	**Study Endpoints**	**Treatment Duration/ Follow Up**	**No. of patients enrolled**	**Study Population**	**No. of Centers and Countries**
PA 16497	Open-label, multi-center, study to assess the pharmacokinetics and safety of oral MMF in the late post-transplant periods	Stable MMF dose per center practice for at least 7 days to achieve steady state PK. MMF dose range 202-424 mg/m^2 twice daily. Mean MMF dose/kg was 12.9 mg/kg.	• Dose finding study to assess PK in pediatric liver transplant recipients and safety and tolerability of MMF in this population	14-16 days after PK sampling day	9	Pediatric liver transplant recipients at least 6 months post-transplant	U.S.

7.2. Review Strategy

As stated in section 6.1, "The goal of the present efficacy supplement (NDA 050722/S-049, 050723/S-049, NDA 050759/S-054) is to add indications for the prophylaxis of organ rejection in pediatric heart and pediatric liver transplant recipients aged 3 months and older." The clinical studies listed in section 7.1 (**Table 17**) provide support for extrapolation of efficacy and dosing from the approved populations including adult kidney, heart, or liver transplant recipients and pediatric kidney transplant recipients, and were reviewed under these prior applications. The only clinical study that was submitted with this sNDA and not reviewed under a prior approval application is an open-label, PK Study, PA 16497, which is discussed and reviewed in detail in section 6.2.1, Pharmacology and Clinical Pharmacokinetics.

The FDA 2019 Draft Guidance on "Substantial Evidence for Effectiveness" provides support for the Agency's review strategy for this sNDA. The guidance states:

> C. Meeting the substantial evidence standard for a new population or a different dose, regimen, or dosage form, based on reliance of FDA's previous finding of effectiveness of an approved drug when scientifically justified and legally permissible.
>
> - The effectiveness of a drug for pediatric use can sometimes be based on FDA's previous finding of effectiveness of the drug in adults, together with scientific evidence that justifies such reliance.[26] In this case, the scientific evidence may include, for example, evidence supporting a conclusion of similar disease course and pathophysiologic basis in adult and pediatric populations, and similar pharmacologic activity of the drug in adults and children (e.g., similar concentration-response relationships), as well as similar blood levels of the drug in adults and children."[1]

Thus, this sNDA is based on the following premises: that the mechanism of transplant rejection in adult and pediatric patients is similar and that MMF prevents rejection by similar mechanisms in adult and pediatric patients.

The review strategy to support efficacy and the proposed dosing for both of the proposed indications is based on the following:

- Extrapolation of efficacy from adult kidney, heart, or liver transplant recipients and pediatric kidney transplant recipients.
- Established PK relationships among the approved populations derived from information in prior approval packages. See section 6, Clinical Pharmacology, for a thorough and detailed description of these relationships.
- For pediatric liver transplant recipients, support is also derived from a comparison of PK derived from study PA 16497 with PK in the approved populations.
- For pediatric heart transplant recipients, supportive evidence is also provided from the literature.

- Data from SRTR/OPTN for heart and liver transplantation in the U.S. provide context for interpretation of the available literature data.

Outstanding Issues:

- No PK study has been conducted in pediatric heart transplant patients. Therefore, in this population, PK data has been extrapolated from the approved adult and pediatric transplant populations. As explained in section 6.1 of Clinical Pharmacology of this review, adult kidney transplant patients and adult heart transplant patients given the same dosage of CellCept demonstrated similar MPA exposures. Further, pediatric kidney transplant and adult kidney transplant patients, at their respective approved doses, demonstrated similar MPA exposures. Hence, MPA exposures at the proposed dosage are expected to be similar in pediatric heart and adult heart transplant patients allowing for extrapolation of efficacy and dosing.

- For pediatric patients 3 months to 2 years, there is limited PK data from the approved clinical studies. Concern regarding ontogenetic changes in IMPDH and deficiency of UGT in this age group suggests efficacy of MMF in this age group may be adversely effected. However, as noted in section 6.1 of this review, PK data in pediatric kidney transplant patients did not demonstrate age-related trends in exposure. In addition, the same BSA based dosing regimen achieved comparable exposures across age groups. As such, there is no evidence that a higher dose is required for patients under 2 years of age.

Dosing rationale:

According to the Clinical Pharmacology review in section 6.2.2, the proposed initial dose of 600 mg/m^2 may be appropriate in pediatric heart and liver transplant recipients 3 months and older based on the prior approval in pediatric kidney transplant recipients aged 3 months and older. For pediatric liver transplant recipients, support of efficacy for doses up to 900 mg/m^2 are derived from PK comparisons between the pediatric liver transplant population and the approved adult and pediatric kidney population. For pediatric heart transplant recipients, support of efficacy for the proposed maximum dose of 900 mg/m^2 is supported by PK comparisons to the approved populations and from literature studies.

The published studies described in section 8.1 report similar outcomes of efficacy (i.e., patient survival and acute rejection) over a wide range of doses and age ranges for both proposed populations. Specifically, for pediatric heart transplant recipients, as PK information is limited, six studies submitted in support of pediatric heart transplant efficacy report including patients under 2 years of age. However, subject level data are not provided and specific dosing for specific age groups cannot be extracted. Given that MMF is already extensively used off-label in pediatric heart transplant and liver transplant recipients, the proposed labeling for patients aged 3 months to under 2 years of age will permit flexibility based on the current use in clinical practice.

Lastly, the Applicant proposed (b) (4)

The Agency does not agree with this proposal (b) (4)

The review strategy for safety of MMF in the proposed populations is discussed under section 8.2, Safety review approach.

Clinical Recommendation: Based on the above evidence and discussions with PeRC, this reviewer considers the evidence of efficacy submitted in support of this sNDA acceptable for the approval of MMF in pediatric heart and liver transplant recipients.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Extrapolation of the Efficacy and the Dosing from the Approved Populations to the Current Pediatric Populations

As stated in section 7.2, Review Strategy, the current sNDA relies on extrapolation of efficacy from the approved adult (i.e., kidney, heart, and liver) and pediatric (i.e., kidney) transplant populations to the proposed pediatric heart and pediatric liver transplant populations. In addition, the 2019 FDA guidance on Substantial Evidence of Effectiveness allows for " inclusion of pediatric use information in labeling without controlled clinical trials of the use in children. In such cases, a sponsor must provide other information to support pediatric use, and the Agency must conclude that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit extrapolation from adult efficacy data to pediatric patients." [1]

Extrapolation of efficacy

The 2019 FDA guidance on Substantial Evidence for Effectiveness, section IV.C, states:

> "The rule revising the Pediatric Use section of product labeling (21 CFR 201.57(f)(9)(iv)) makes allowance for inclusion of pediatric use information in labeling without controlled clinical trials of the use in children. In such cases, a sponsor must provide other information to support pediatric use, and the Agency must conclude that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit extrapolation from adult efficacy data to pediatric patients. Evidence that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes evidence of common pathophysiology and natural history of the disease in the adult and pediatric populations, evidence of common drug metabolism and similar concentration-response relationships in each population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions."[1]

The premise of this application is that the mechanism of transplant organ rejection is similar across different organs, in adults and children, and that similar drug exposure in pediatric patients as in adults will lead to the same therapeutic effect (i.e., a reduction in the risk of acute rejection).

This sNDA relies on the following for substantial evidence of effectiveness:

- The mechanism of rejection is similar across all organs and age groups
- The extrapolation of efficacy from the pivotal studies for the approved adult indications (Studies ICM 1866, MYC023, and MYC022 in Adult Kidney Transplant; Study MYCS 1865 in Adult Heart Transplant; Study MYCS2646 in Adult Liver Transplant)

- The extrapolation of efficacy from the approved pediatric kidney transplant indication (supported by the pediatric kidney transplantation studies MYC 2190 and MYCS 2675).
- The ontogeny of IMPDH is suggested to be complete by 2 years of age. It is unclear whether there may be ontogenetic differences in IMPDH in children younger than 2 years of age that would impact MPA activity in this age group. See section 6.2 for detailed information and discussion
- Evidence of efficacy from published literature of the use of CellCept in pediatric heart and pediatric liver transplant recipients
- Supporting data from the Scientific Registry of Transplant Recipients (SRTR)/ Organ Procurement and Transplantation Network (OPTN) database
- One PK study in pediatric liver transplant recipients (PA 16497)

As summarized in section 6.1 of the Clinical Pharmacology section, exposure relationships between pediatric kidney transplant and pediatric liver transplant populations are similar to those seen between the adult kidney and adult liver transplant populations. Thus, "the efficacy of CellCept in pediatric liver transplantation [can] be extrapolated from adult transplantation based on the comparable CellCept exposure." (section 6.1, Executive Summary).

Similarly, for pediatric heart transplant patients, in section 6.1 the Clinical Pharmacology reviewer notes that exposure relationships between adult kidney and adult heart transplant patients, at the same CellCept dose, as well as between pediatric kidney and adult kidney transplant patients, at their respective approved doses, allow for extrapolation of efficacy and dosing to the pediatric heart transplant population. Based on these relationships, MPA exposure at the recommended dosage is expected to be similar in pediatric heart transplant and adult heart transplant patients. Therefore, "the efficacy of Cellcept in pediatric heart transplantation [can] be extrapolated from adult heart transplantation data based on the estimated comparable CellCept exposure." (section 6.1 Executive Summary, Clinical Pharmacology).

See Clinical Pharmacology section 6.2 and 6.3 for a detailed and thorough analysis of extrapolation of efficacy for the pediatric heart and liver transplant populations.

<u>Uncertainties for pediatric heart and pediatric liver transplant patients less than 2 years of age:</u>

Ontogeny of IMPDH

CellCept is the pro-ester drug of mycophenolic acid (MPA) and, following oral administration, conversion to MPA is nearly complete. MPA selectively and reversibly inhibits IMPDH, which is the committed step in de novo guanosine nucleotide biosynthesis.

It is unclear if IMPDH undergoes ontogenetic changes in children below 2 years old that would impact MPA activity in this age group. A study by Rother et al 2012[5] analyzed peripheral blood mononuclear cells (PBMCs) in 80 healthy children between the ages of 2 to 18 years and did not

find any developmental regulation of IMPDH activity in children over 2 years of age. Children under 2 years of age were not evaluated in this study, however, and no additional information has been provided to describe IMPDH expression and activity in this age group.

Ontogeny of glucoronyl transferase

MPA is metabolized principally by uridine diphosphate glucuronosyltransferase (UGT) to form the phenolic glucuronide of MPA (MPAG). MPA plasma concentrations are dependent on metabolism via glucuronidation, which leads to enterohepatic recirculation following MPAG secretion in bile and glucuronide cleavage. As noted in section 6.3.2, the activity of UGT enzymes is deficient at birth and absent from the fetal liver, but increases to reach adult levels by approximately 2 to 4 years of age. It is unclear how and to what extent deficient UGT activity may contribute to differences in MPA exposure in children younger than 2 years of age.

Conclusions regarding uncertainties

Despite the potential uncertainties identified in children under 2 years of age, section 6.3.2 of Clinical Pharmacology identifies data suggesting that MPA exposure may be similar in this age group as compared with older age groups. Specifically, the Clinical Pharmacology reviewer notes that MPA AUC_{0-12} in pediatric kidney transplant patients under 2 years of age (Study MYCS 2675) was numerically lower relative to older age groups, but that an analysis of MPA AUC versus continuous age did not suggest an age-related trend in exposure. It is also noteworthy that the 600 mg/m^2 BID dosage was approved in all pediatric kidney transplant patients down to 3 months of age and most pediatric liver transplant patients in Study PA 16497 (6 of 8) were under 2 years of age. High inter-patient variability in MPA exposure in Study PA 16497 was described.

Overall, the available data in pediatric kidney transplant and pediatric liver transplant patients suggests that MPA exposure after MMF dosing remains approximately consistent across pediatric patients including in those younger than 2 years of age. Despite high inter-individual variability in exposure with MMF dosing, in current clinical use, the dose may be modified based on clinical factors such as tolerability, concomitant medications, and laboratory parameters. Given the widespread off label use of MMF in the pediatric heart and pediatric liver transplant populations and clinical efficacy (see discussion of published studies in section 8.1) over the past 20 years, the proposed labeling for all patients including those aged 3 months to less than 2 years of age, will permit flexibility in dosing at the clinician's discretion based on established clinical practice.

<u>Dose rationale for pediatric heart and pediatric liver transplant indications:</u>

The proposed oral MMF dosing regimen for pediatric heart transplant and liver transplant patients is a starting dose of 600 mg/m^2 up to a maximum of 900 mg/m^2 twice daily (BID). The proposed dosing parallels the recommended oral MMF dosage in adult kidney transplant

patients (1 g BID) relative to that for adult heart transplant and liver transplant patients (1.5 g BID).

For the adult kidney transplant program, Study MYC 058 determined that an MPA $AUC_{0\text{-}12h}$ of 27.2 h·mg/L, which corresponded to a dose of 1 gram BID, was the target value that provided an optimal benefit for the prevention of acute rejection with an acceptable safety profile, in the early post-transplant period.

MPA PK after MMF dosing in adult heart transplant patients has been shown to be similar to that in adult kidney transplant patients. The rationale for increased MMF dosage that was in the original studies leading to approval in adult heart transplant patients compared to adult kidney transplant patients was to prevent loss of the life-sustaining heart allograft. MPA PK after MMF dosing in adult liver transplant patients was noted to be lower than that in adult kidney transplant patients at the same dose. As a result, adult liver transplant patients have higher dosing needs to achieve a similar MPA exposure to that in kidney transplant patients. The lower exposure in adult liver transplant recipients provides the rationale for increasing the MMF dosage in this population.

For the pediatric kidney development program, Study MYC 2190, the initial dose-finding study, determined that 23 mg/kg BID dosing provided MPA $AUC_{0\text{-}12}$ exposures closest to the adult kidney transplant approved dose of 1 g BID and was terminated early. In addition, substantial inter-individual variation in MPA AUC was observed with body weight dosing with approximately 10% lower coefficient of variation determined based on a BSA based dosing analysis; thus, BSA based dosing was recommended.

It is important to note that all studies in the CellCept development program included cyclosporine (CsA) and corticosteroids as part of the immunosuppressive regimen. Later on, it was determined that cyclosporine interferes with the enterohepatic circulation (EHC) of MPA. CsA inhibits multidrug resistance protein 2 (MRP 2), thereby, inhibiting the secretion of MPAG into the bile and EHC. Thus, higher doses of MMF are required when dosed with CsA. Tacrolimus, a second generation CNI, does not interfere with MMF EHC and does not have a similar effect on MPA exposure.

According to the Clinical Pharmacology review in section 6.3.2:

> "The available clinical pharmacology data, described in previous sections, has provided evidence suggesting that PK relationships across pediatric transplant populations mimics those observed across adult transplant populations. This includes similarity in PK between kidney transplant and heart transplant patients, and lower exposure at the same dose in liver transplant patients relative to kidney transplant patients. The proposed minimum dosage of 600 mg/m^2 BID has precedence as the recommended dosage in kidney transplant patients. The proposed maximum dosage of 900 mg/m^2 BID represents a 50% increase over the minimum dosage and arithmetically matches the increase in the dosage recommended for adult heart transplant and liver transplant

patients. Given the high inter-individual variability in MPA exposure after MMF dosing and the potential for increased adverse events at the highest dose, proposing a range between 600 and 900 mg/m^2 appears appropriate from a clinical pharmacology perspective."

Clinical recommendation: This Clinical reviewer agrees with the Clinical Pharmacology reviewer that the proposed dosing for the pediatric heart and liver transplant populations appears appropriate and reasonable.

8.1.2. The Applicant Sponsored Clinical Studies for the Approved Indications:

Clinical study reports and datasets are not available for the following Applicant conducted clinical studies as these were reviewed under prior approval packages. They were conducted almost 30 years ago. Information is obtained from the Summary of Clinical Efficacy included in the sNDA submission.

Adult kidney transplant clinical studies:

Studies ICM 1866/MYC023/ MYC022: CellCept was first approved for the prophylaxis of allograft rejection in adult kidney transplant recipients based on three randomized, double-blind, multicenter trials demonstrating the safety and efficacy of MMF in combination with corticosteroids (CS) and CsA (i.e., ICM 1866, MYC022, MYC023). These three studies compared two dose levels of MMF (1 g twice a day (BID) and 1.5 g BID) to azathioprine (AZA) (ICM 1866 and MYC023) or placebo (MYC022). See **Table 17** for specific dosing regimens in the adult kidney transplant studies.

The primary efficacy endpoint for each study 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, or the occurrence of death or graft loss, or early termination from the study for any reason without prior biopsy-proven rejection.

MMF in combination with CS and CsA significantly reduced the incidence of treatment failure within the first 6 months following transplantation ($p<0.05$). Yet, more patients receiving MMF discontinued therapy (without prior biopsy-proven rejection, death, or graft loss) than in the control groups, with the highest discontinuation rate in the MMF 3 g/day group. Patients in all treatment groups who terminated early were found to have a higher incidence of graft loss and death at 12 months post transplantation. Nonetheless, the twelve month incidence of graft loss and patient deaths was lower for both MMF groups compared to the controls in all three studies. Long-term results with up to three years of follow-up showed better outcomes in the MMF treated groups compared to controls as well.

Adult heart and adult liver transplant clinical studies:

Study MYCS 1864 (adult heart transplant): This study assessed an MMF dose of 1.5 g BID that was determined from a small, uncontrolled, dose-finding study in heart transplant recipients. The comparator was AZA (1.5-3 mg/kg/day), and 578 heart transplant recipients were evaluated. No statistical difference with respect to biopsy-proven rejection with hemodynamic compromise (p=0.338) was found. However, 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% CI: 1.1 to 12.0%), suggesting a patient and graft survival benefit for MMF.

Study MYCS2646 (adult liver transplant): This study was a randomized, double-blind, multi-center, parallel-group study that compared intravenous (IV) MMF followed by 1.5 g BID oral MMF to IV AZA followed by 1-2 mg/kg/day oral AZA. Five-hundred sixty-four (564) primary liver transplant recipients were evaluated. This study showed fewer treatment failures (biopsy-proven rejection, treated rejection, or death /retransplantation) for MMF compared to AZA at 6 months (38.1% vs 47.7%), 12 months (42.4% vs 50.2%), and 3 years (48.9% vs 47.7%).

Pediatric kidney transplant clinical studies:

Study MYC 2190: This study was a pilot, PK, dose-finding study using CellCept capsules to determine the PK of MPA and MPAG and optimal dose in 40 patients 3 months through 18 years of age. Target MPA $AUC_{0\text{-}12h}$ of 27.2 µg·h/mL was derived from the PK/PD Study MYC 058 in adult kidney transplant patients that was associated with the 1 g BID dose for adult kidney transplant recipients in the early post-transplant period.

In this non-randomized, multicenter, open-label study each patient was stratified to one of 3 age groups (less than 6 years; 6 years to less than 12 years; and 12 to 18 years;) and received 1 of 3 dose levels of oral MMF (15 mg/kg BID, 23 mg/kg BID, or 30 mg/kg BID) for the prevention of kidney allograft rejection. Patients also received concomitant CsA and CS but not AZA. In this study, the 23 mg/kg BID dose most closely achieved the adult target MPA $AUC_{0\text{-}12h}$ of 27.2 µg·h/mL. The study was originally intended to last for 3 years but was terminated early once the target dose was determined. The 23 mg/kg BID dose was then assessed in a follow-up study (MYC 2190 V2) in which patients could continue on this MMF dose until they had completed 3 years on MMF.

The dose selected from Study MYC 2190 was then subsequently tested in the pediatric pivotal Study MYCS 2675.

Study MYCS 2675: This pivotal study was conducted in 100 pediatric kidney transplant recipients from 3 months of age to 18 years. A dose extrapolated from the adult kidney transplant data, 600 mg/m^2 up to a maximum of 1 g BID, was assessed in combination with CsA and CS in this single-arm, open-label study for a duration of up to 3 years post-transplant. This study showed biopsy proven graft rejection rates of 24% and 25% at 6 and 12-months post-

transplant, respectively. Graft and patient survival of 93% at both time points were also excellent and comparable to the adult populations.

Conclusion: These Applicant conducted clinical studies demonstrate the efficacy of MMF in the approved populations in combination with cyclosporine and corticosteroids. CsA is now known to interfere with the EHC of MMF, thereby, resulting in higher dosage requirements. The exposure relationships and dosing rationale detailed in the Clinical Pharmacology section 6 and summarized in sections 7 and 8.1, permit extrapolation of efficacy and dosing to the proposed pediatric heart and pediatric liver transplant populations aged 3 months and older. Though there are uncertainties in patients less than 2 years of age, as described above, an analysis of MPA AUC versus continuous age did not suggest an age-related trend in exposure, and the pediatric kidney transplant approval in patients down to 3 months of age provides precedent and support. Also, clinical study and PK data in pediatric heart transplant patients under 2 years of age may be limited, but the published studies indicating 20 years of use and SRTR/OPTN data provide additional support for efficacy in this population. Published studies will be discussed below.

Overall, this clinical reviewer finds the extrapolation of efficacy and dosing for the pediatric heart and pediatric liver transplant populations reasonable for approval.

8.1.3. Published Literature in Support of Efficacy of MMF in Pediatric Heart and Pediatric Liver Transplant Recipients

Summary of search criteria and study designs

The Applicant conducted a systematic literature search across electronic databases BIOSIS Previews, Derwent Drug File, Embase, Medline, Cochrane Library, and NICE cumulative until June 8, 2021. Search terms and criteria are listed in the Applicant's Summary of Clinical Efficacy.[6] One hundred and five (105) publications were identified and screened further by the Applicant. Fourteen studies (14) in pediatric heart transplant and fifteen studies (15) in pediatric liver transplant were submitted in the clinical module (Module 5) in support of clinical efficacy.

The published studies are small in size, mostly retrospective, with a few prospective studies, and were not designed to demonstrate efficacy. Study publications date back to 2001 (Dipchand et al). Some studies compare outcomes before the introduction of MMF and other studies compare outcomes after the introduction of MMF into the standard of care immunosuppressive (IS) regimen. Because the studies include MMF as part of a combined IS regimen, it is not possible to directly attribute the observed outcomes to MMF. In addition, many of the studies use limited descriptive statistics.

The lack of multicenter, randomized controlled trials in pediatric heart and pediatric liver transplant patients, has resulted in several centers establishing institutional practices regarding

transplant IS based on clinical experience. Despite these limitations, the regimens containing MMF consistently indicate that MMF is effective for the proposed pediatric heart and pediatric liver transplant indications.

Pediatric heart transplant published studies

Prior to 1999, the majority of pediatric heart transplant recipients were maintained on a triple regimen of CsA, AZA, and prednisone. After 2000, the most common regimen became tacrolimus and MMF with or without steroids.

Outcomes for pediatric heart transplant recipients have improved since the initial approval of CellCept, partly due to better efficacy of MMF compared to AZA. A 23 year, retrospective, single-center study in 180 pediatric heart transplant recipients by Tuite et al 2021[7] reported on 1, 5, and 10 year survival rates after the adoption of MMF. Survival rates were improved at every timepoint. This study supports the observation that MMF has contributed to improved survival after heart transplantation.

Published studies describing acute rejection rates

Acute rejection is a major contributor to the morbidity and mortality in children after heart transplantation. Four studies assessed the prophylaxis of organ rejection with MMF in children under 17 years of age after heart transplant. Groetzner et al 2005,[8] Lammers et al 2010,[9] Lamour et al 2019,[10] and Marshall et al 2013,[11] made similar conclusions that switching from AZA to MMF results in a larger percentage of patients free from acute rejection. Reported rates of rejection ranged from 13-36%.

Published studies describing other potential safety benefits of MMF use

Steroid minimization or withdrawal is also of great interest in this population, given the adverse effects associated with long term steroid use including growth restriction, hypertension, glucose intolerance, weight gain, and osteoporosis. Three studies assessed steroid reduction or withdrawal with an MMF regimen. Dipchand et al 2001,[12] Lamour et al 2019,[10] and Singh et al 2010[13] concluded that MMF can facilitate steroid reduction or withdrawal with low rejection rates and favorable survival (freedom from acute rejection 78.6%-92%). According to the Applicant, these studies also show that an MMF based regimen permit corticosteroid reduction or withdrawal with acceptable rejection rates during the first year post transplant in pediatric heart transplant recipients.

As with chronic steroid use, chronic CNI use results in multiple comorbidities. Of particular concern is CNI associated kidney dysfunction, which can impact graft and patient survival. Safely improving renal function to limit the effects of chronic kidney disease and subsequent end stage kidney disease is particularly important in children who may face the prospect of needing a kidney transplant because of their immunosuppression regimen. Boyer et al 2005[14]

demonstrated an improvement in both glomerular and tubular kidney function in 14 children who underwent CNI dose reduction after MMF was introduced. They measured inulin and creatinine clearance, which improved soon after the switch to MMF and persisted for one to two years. The authors concluded that replacing AZA with MMF can allow for CNI reduction and improve renal function without an increase in the incidence of acute rejection (11 / 14 (78%) remained free of acute rejection at 1 year) or number of adverse events. A retrospective study by Rosenthal et al 2021[15] also demonstrated that a regimen of MMF and everolimus can improve kidney function without an increase in organ rejection or death.

Use of MMF in pediatric heart transplant patients less than 2 years old:

Six studies submitted with the sNDA for pediatric heart transplant indication include patients under 2 years of age. The studies vary by design, objective, dosing and endpoints. Age range of the participants was provided for most of the studies and spans from as young as 4 days old to 22 years old. Doses, however, were either not specified or wide ranges using body weight or BSA based dosing were reported. In addition, subject level data on dosing and outcomes in patients less than 2 years old is not available. Nonetheless, it is assumed that the authors' conclusions apply to all the age groups included in the studies.

For example, Groetzner et al 2005[8] conducted a single center retrospective study from 1988-2002 in 47 pediatric patients after heart transplantation with a mean age of 9.4 years but a range of 4 days to 18 years. The authors concluded that graft survival improved after the introduction of MMF (1995) to 92% at 1 year from 78% and that 5 year survival improved to 80% from 68% (p=.04). They did not find that age was a predictor for survival. They also reported that MMF in combination with CNIs (started after 1995) had a significantly higher rate of freedom from acute rejection compared to azathioprine in combination with CNIs (62% vs 40%, p=.0013).

In addition, Singh et al 2010[13] conducted a retrospective study in 55 pediatric patients after heart transplantation assessing a steroid avoidance protocol. The children ranged in age from 2 weeks to 22 years, with a median age of 7.1 years. The authors reported that the risk of rejection was less than 10% during the first six months due to the new regimen and that post-transplant survival at 6 months was 91% and at 12 months was 88%.

<u>Pediatric liver transplant published studies:</u>

According to 2019 SRTR data, graft survival among pediatric liver transplant recipients has improved over the last decade. For pediatric liver transplants performed in 2012-2014, overall five year patient survival was 89.3% and ten year survival was over 80%. In addition, rates of graft survival for children are similar to adults up to 3 years post liver transplant, and, from 3-10 years post-transplant, children show improved survival compared to adults. For example, in 2019, ten year pediatric liver transplant recipient mortality was 18.2% versus 39.5% for adult liver transplant recipients.[16]

Published studies describing acute rejection rates

Late acute and chronic rejection continue to negatively impact long term outcomes in pediatric liver transplants. Yazigi et al 2013[16] report that approximately 60% of pediatric liver transplant recipients experience acute cellular rejection within the first few years after transplant.

In support of the use of MMF for the prophylaxis and treatment of liver transplant rejection, the Applicant submitted two studies by Chardot et al 2001[17] and Aw et al 2008.[18] Chardot et al 2001 published a retrospective analysis of a single-center experience in France that used MMF in 19 pediatric liver transplant patients for various indications. They report the use of MMF for the treatment of acute rejection or insufficient immunosuppression in 16 patients resulted in normalization of liver function tests in 10 out of 16 (10/16, 62%) patients.

Aw et al 2008[19] evaluated the long-term outcomes of 26 pediatric liver transplant recipients who were treated with MMF for steroid resistant rejection (SRR) from September 1996 to December 1999. Patients were then followed prospectively for outcomes until August 2007. The standard immunosuppression regimen was CsA based in 22 patients and tac based in 6 patients. Twenty-one of 28 episodes (21/28, 75%) of SRR treated with MMF responded with improving or normalized liver function tests (LFTs).

In addition, a study by Leiskau et al 2018[23] reported favorable efficacy outcomes with the use of MMF. The authors assessed de-novo initiation of MMF with tac after pediatric liver transplantation and compared this regimen to diagnosis matched controls treated with tac monotherapy or CsA plus steroids. The authors reported a graft survival at 1 year of 89.5% in the MMF plus tac group and a biopsy proven acute rejection rate of 31.5% in the MMF plus tac group compared to 42.1% for the CSA plus steroids group. Though these rates were not statistically significant (p>.05), they do indicate that MMF results in comparable efficacy rates to prior approved regimens.

Published studies describing other potential safety benefits of MMF use

As with pediatric heart transplant recipients, long term immunosuppression use leads to several comorbidities in pediatric liver transplant recipients as well. For example, renal dysfunction associated with chronic CNI use is also a major concern for pediatric liver transplant recipients. The Applicant submitted five studies describing the renal benefit of MMF in pediatric liver transplant recipients.

The studies by Aw et al 2001,[19] Nobili et al 2003,[20] Ferraris et al 2004,[21] Evans et al 2005,[22] and Tannuri et al 2021[23] assess the use of MMF as an adjunctive agent to reduce CNI exposure. They are small and prospective or retrospective studies without a consistent control across the studies. Nonetheless, they all conclude that CNI dosage could be reduced with the addition of MMF in pediatric liver transplant recipients without the loss of efficacy. For example, where

reported, rates of acute rejection were comparable to those seen in the pivotal studies for the approved indications.

In contrast, the study by Leiskau et al 2018[24] also measured kidney function by estimated GFR or creatinine after one year of treatment with MMF and did not find a significant improvement in renal function as measured.

Lastly, steroid reduction or minimization is also of interest in pediatric liver transplantation because of the adverse effects associated with chronic steroid use. An abstract by Teisseyre et al 2011[25] describes a steroid sparing benefit of MMF in pediatric liver transplantation. The authors reported on the three year follow up of a study comparing tac plus MMF and tac plus steroids in pediatric liver transplant recipients. Steroids were minimized according to a low-dose scheme and then withdrawn starting at 7 months post-liver transplant. The tac plus MMF arm had frequent acute rejection episodes at year 2 after transplant, but steroid resistant acute rejection was not observed in either group.

Summary of published literature and SRTR data in support of efficacy for pediatric heart transplantation

According to the SRTR/OPTN Annual Data Reports for Heart and Liver Transplantation,[6, 16] pediatric heart transplants have been rising for the past 10 years with pediatric liver transplants remaining steady in the mid 500s.

The SRTR Annual Report for Heart and published studies by Marshall et al 2013[11] and Castleberry et al 2017,[26] report that the majority of pediatric heart transplant recipients were maintained on a regimen of CsA, AZA, and steroids from 1994-1999. Marshall et al[11] and Castleberry et al[26] report that the common IS regimen changed to tac plus MMF during the period of 2001-2010.

Similar trends with increased use of MMF in immunosuppression regimens for pediatric liver transplant were also seen. This transition coincides with the approval of MMF for the prophylaxis of organ rejection in adult kidney, heart and liver transplant recipients and pediatric kidney transplant recipients.

Published studies in both pediatric heart and pediatric liver transplant patients show acceptable and, in some cases, better rates of acute rejection compared to AZA. Changes in immunosuppression regimens including the addition of MMF have also been associated with improved patient and graft survival up to 10 years post-transplant. Despites these improvements in pediatric heart transplant outcomes, significant morbidity and mortality remain with long term immunosuppression use. The Applicant has submitted several studies, as noted above, that also describe the benefit of MMF in stabilizing renal function and reducing chronic steroid use. However, these benefits have not been verified by the FDA in approved clinical trials. Nonetheless, with all the benefits noted, the published studies provide support

for the use of MMF for the prophylaxis of organ rejection in the pediatric heart and pediatric liver transplant populations.

Overall conclusions of efficacy and dosing based on extrapolation, published literature, and SRTR/OPTN data

The available clinical pharmacology data, described in previous sections, provide evidence suggesting that PK relationships across pediatric transplant populations mimics those observed across adult transplant populations; thus, support for extrapolation of efficacy and dosing from the approved populations to the proposed populations is reasonable. The Applicant conducted clinical studies in adult kidney, heart, and liver transplant and pediatric kidney transplant patients demonstrate the efficacy of MMF in combination with cyclosporine and corticosteroids in these populations. CsA is now known to interfere with the EHC of MMF, resulting in higher dosage requirements.

The proposed minimum dosage of 600 mg/m^2 BID has precedence as the approved dosage in pediatric kidney transplant patients. The proposed maximum dosage of 900 mg/m^2 BID matches the increase in the dosage recommended for adult heart transplant and liver transplant patients.

Concerns identified in the previous sections include limited clinical study and PK data in pediatric heart transplant patients less than 2 year old. Uncertainties such as possible ontogenetic changes in IMPDH and deficiency in UGT, is also discussed. High inter-individual variability in exposure with MMF dosing is also described in prior sections. Nonetheless, the available data in pediatric kidney transplant and pediatric liver transplant patients suggests that MPA exposure after MMF dosing remains approximately consistent across pediatric patients including in those younger than 2 years of age. Also, high inter-individual variability can be clinically managed with dose adjustments based on factors such as tolerability, concomitant medications, and laboratory parameters.

The widespread off label use of MMF with satisfactory outcomes noted in the SRTR data and published studies from the past 20 years also support the clinical efficacy of MMF in the pediatric heart and pediatric liver transplant populations. Overall, this clinical reviewer finds the evidence in support of efficacy and dosing for the pediatric heart and pediatric liver transplant populations reasonable for approval. The proposed labeling for all patients including those aged 3 months to less than 2 years of age, will permit flexibility in dosing at the clinician's discretion based on established clinical practice.

8.2. Review of Safety

8.2.1. Safety Review Approach

As noted earlier in this Unireview, CellCept was initially approved for use in 1995. According to SRTR/OPTN data, MMF is now used in combination with other immunosuppressants in the

majority of pediatric heart and liver transplant recipient IS regimens. The Applicant submitted this sNDA to add the pediatric heart and pediatric liver transplant indications to the CellCept labeling in response to an Agency request to consider such an update in December 2018. The Applicant has not conducted any new clinical trials to support the safety of MMF in the prophylaxis of organ rejection in pediatric heart and pediatric liver transplant recipients.

This safety review is based on support from:

- Study MYC 2190 and Study MYCS 2675, the two pediatric kidney transplant studies reviewed under the approval package for the pediatric kidney transplant indication.
- PK Study, PA 16497, in pediatric liver transplant patients, which is the only new study submitted with this sNDA and not reviewed under a prior application.
- Safety data from publications describing the use of MMF in pediatric heart and pediatric liver transplant patients.
- Review of safety data from Applicant's post-marketing safety database.

Clinical studies:

The Applicant conducted two studies in pediatric kidney transplant patients, Study MYC 2190 and Study MYCS 2675. The pediatric liver transplant study is PA 16497. No pediatric studies have been completed in pediatric heart transplant recipients.

Publications:

Twelve clinical studies relevant to pediatric heart transplant and 22 studies relevant to pediatric liver transplant were submitted in support of this sNDA. According to the Applicant, these 34 publications provide relevant safety information in approximately 295 pediatric heart transplant recipients and 976 pediatric liver transplant recipients. The Applicant acknowledges several limitations of these studies including limited details on the age of each patient, the number of patients exposed to MMF, and the duration of exposure.

In the pediatric heart transplant studies, the ages and pediatric age groups vary widely from newborn (4 days old, Groetzner et al 2005[8]) to young adult (22 years old, Singh et al 2010[13]). Studies in a specified age group (i.e., newborns, infants, or toddlers) were not identified. In addition, reported AEs from the publications could not be linked to a particular patient or treatment regimen as clinical study reports were not available to the Applicant. In pediatric liver transplant, limitations of the available data are similar.

Dosing and formulation were not reported in most of the studies. Duration of use also varied from 1 year to 8 years.

Company safety database:

The Applicant also conducted an analysis of the company's safety database with specifics of data retrieval noted in section 8.2.2 of this Unireview.

The Applicant acknowledges the limitations of their approach including the small dataset for pediatric patients and a large difference in available data for pediatric heart and liver transplant recipients compared to adult heart and liver transplant recipients. Moreover, post marketing reports are also subject to reporting bias and underreporting. With these caveats in mind, the comparisons indicate that the safety profile of pediatric heart and liver transplant recipients are largely similar to their adult counterparts. For example, the common adverse reactions of diarrhea, leukopenia, infection, and vomiting were reported in the pediatric heart and liver transplant populations as well. Similarly, the warnings and precautions of blood dyscrasias, gastrointestinal complications such as ulcerations and perforations, lymphomas including PTLD, and serious infections such as cytomegalovirus infections (CMV), and Epstein-Barr Virus (EBV) infections were also reported in these populations.

Conclusion: Overall, no new safety signals have emerged from this Clinical Reviewer's review of the safety information from the clinical studies, published studies, and the Applicant's post-marketing safety database. The review of safety for the use of MMF in the pediatric heart and pediatric liver transplant populations is reasonable to support approval of this sNDA.

8.2.2. Review of the Applicant Safety Database

The Applicant analyzed data from their company safety database (Roche Global Safety Database) from the date of approval May 3, 1995 to March 31, 2021. All sources of AEs and all AEs, regardless of causality, were considered.

Overall exposure

The Applicant notes that from 1995 to 2021 the estimated cumulative post-marketing exposure of MMF to all patients regardless of age or indication (i.e., both off-label and on-label use) was 8.38 million patient-years.

Specific to organ transplant, individual case reports in the Applicant's safety database retrieved 335 individual case safety reports (ICSR) comprising 1,141 AEs for pediatric kidney transplant patients; 60 ICSRs comprising 171 AEs for pediatric heart transplant patients; and 91 ICSRs comprising 221 AEs for pediatric liver transplant patients.

Of the 60 cases reported in pediatric heart transplant, the majority of cases were reported in children 2-12 years old (32 cases, 53.3%). Eleven cases (18.3%) were reported in children 1 month to 2 years old. For pediatric liver transplant, of the 91 cases reported, 47 cases were in children 2-12 years old (51.6%), 13 cases in infants 1 month-2 years (14.3%), and 2 cases (2.2%) in neonates (birth to 1 month).[5]

In the Applicant's Clinical Summary of Safety submitted with the sNDA, they compared the proportion of adverse events (AEs) and serious adverse events (SAEs) in pediatric heart or liver

transplant recipients to adult heart or liver transplant recipients and to pediatric kidney transplant recipients. When an imbalance of >3% was identified between the pediatic and adult system organ class (SOC) or between pediatric heart or liver transplant and pediatric kidney transplant SOC, the Applicant investigated the discrepancy.

A general discussion of the discrepancies categorized by AEs and SAEs for pediatric heart and liver transplant recipients in the Applicant's safety database is described below.

Pediatric heart transplant AEs compared to adult heart transplant and pediatric kidney transplant AEs

AEs by system organ class (SOC) in Applicant safety database compared to adult heart transplant:

Overall, the proportions of all AEs in pediatric and adult heart transplant patients were similar, except for a higher proportion of AEs reported in pediatric patients within the SOCs Neoplasms benign, malignant and unspecified (12.87% vs 3.03%) and Gastrointestinal (GI) disorders (14.04% vs 10.87%). For both of these SOCs, the reported preferred terms (PTs) are well-known adverse drug reactions listed in CellCept's USPI such as PTLD, diarrhea, vomiting, and alopecia.

The higher proportions of the specific SOC's observed in pediatric patients may be attributed to limitations of the applied methodology (i.e., the comparison of proportions) and several reporting biases including solicited reports and duplicates pending resolution. Such biases likely contributed to the large proportional fluctuations in the dataset of pediatric patients, which are smaller in number of reported events. According to the Applicant, no new safety signal emerged from the qualitative and quantitative assessment of the AEs reported in the SOCs with discrepant reporting (i.e., Neoplasm benign, malignant, unspecified and GI disorders).

Conclusion: After review of the Applicant's assessment of the AEs and description of the case reports, this reviewer concurs that no new safety signal has emerged from the Neoplasm and GI SOC.

SAEs by SOC in Applicant safety database compared to adult heart transplant:

The proportions of SAEs were similar among pediatric and adult patients with heart transplant. Two exceptions were a higher proportion of SAEs reported in pediatric heart transplant patients compared to adults for the SOCs Neoplasms benign, malignant and unspecified (18.33% vs 5.33%), and GI disorders (13.33% vs 8.72%).

The reported SAEs are known adverse drug reactions listed in CellCept's USPI including lymphoma, skin malignancy, and gastric ulcer. Though the nature of the reported GI SAEs appears consistent with the established safety profile of MMF, even minor gastrointestinal events may lead to greater seriousness or severity in the pediatric transplant population due to

factors such as gut sensitivity from immunosuppressants and prior surgeries. In addition, as noted in the Medical Officer's review for the pediatric kidney transplant application (NDA 50-722, S-007), pediatric patients <6 years old reported a higher incidence of nausea, vomiting, and diarrhea.

Conclusion: Thus, albeit the limitations of the database described above, this reviewer concludes that no new safety signal has emerged from review of the AEs and SAEs in the Applicant's safety database for pediatric heart transplant compared to adult heart transplant.

AEs by SOC in Applicant safety database compared to pediatric kidney transplant:

As noted in section 8.2.1, 60 cases comprising 171 AEs were retrieved for pediatric heart transplant and 335 cases comprising 1,141 AEs were retrieved for pediatric kidney transplant. Overall, the proportions of all AEs reported in both pediatric heart transplant patients and pediatric kidney transplant patients were similar. There was a notable difference in the reported AEs for the SOC Neoplasms benign, malignant and unspecified, for the pediatric heart transplant indication (22 AEs, 12.87%) compared to the pediatric kidney transplant indication (15 AEs, 1.31%).

The Applicant provided a breakdown of each of the 22 AEs and demonstrated that the majority of the reported AEs for the SOC Neoplasm were lymphomas and smooth muscle cell neoplasms. Lymphomas are an important identified risk in the CellCept USPI, and smooth muscle cell neoplasm can occur more frequently in immunocompromised patients and are often associated with EBV infection.[27]

The reporting biases described in section 8.2.1 also likely contributed here and resulted in a larger proportional impact on the small dataset for pediatric heart transplant candidates. Also, EBV seronegativity in the recipient and higher intensity of immunosuppression or overall immunosuppression are known to be associated with a higher risk of PTLD. Moreover, as reported by Mynarek et al 2013, the rate of PTLD is 1-5% for kidney transplantation and 4-10% for heart or liver transplantation.[28]

Conclusion: The limitations of post-marketing AE reporting described in section 8.2.1, an increased risk of malignancy due to higher immunosuppression load in the pediatric heart transplant population, and higher EBV negative status among children may explain the discrepancy in the proportion of reported AEs. Thus, this reviewer concludes that no new safety signal compared to the pediatric kidney transplant population has emerged from an assessment of AEs for the SOC Neoplasms in the Applicant's safety database.

<u>Pediatric liver transplant compared to adult liver transplant and pediatric kidney transplant</u>

AEs by SOC in Applicant safety database compared to adult liver transplant:

Overall, the proportions of AEs in liver transplant patients reported in both the pediatric and adult age groups were similar. A notable higher proportion of AEs were reported under the SOCs GI disorders (18.10% vs 11.47%) and Investigations (10.86% vs 7.60%) for pediatric liver transplant patients compared to adult liver transplant patients.

For GI disorders, the imbalance was predominantly related to adverse drug reactions such as diarrhea, vomiting, and abdominal pain, which are listed in CellCept's USPI. However, it is important to note that the AE dataset for pediatric liver transplant patients is considerably smaller than that of the adult liver transplant patients (221 AEs vs 4,038 AEs). In addition, several reporting biases such as solicited reports and duplicates pending resolution, likely contributed to the large proportional fluctuations as well.

A review of the cases under the SOC Investigations indicated that many of the laboratory abnormalities are expected post liver transplant surgery including elevated liver function tests (LFTs) and alkaline phosphatase. In addition, other laboratory elevations such as blood lactate dehydrogenase, are known adverse reactions included in the CellCept USPI. Another limitation, as noted above, is that the smaller dataset resulted in larger proportional fluctuations; so, only 24 AEs reported under this AOC comprised 10.86% of the dataset.

Conclusion: Thus, noting the limitations of the database described above, this reviewer concludes that no new safety signal has emerged after a review of AEs in the Applicant's safety database for pediatric liver transplant patients compared to adult liver transplant patients.

SAEs by SOC in Applicant safety database compared to adult liver transplant:

The proportions of SAEs were similar among pediatric liver transplant and adult liver transplant patients except for a higher proportion of AEs in the pediatric population for the following SOCs: GI disorders (18.52% vs 9.41%), Surgical and medical procedures (4.44% vs 0.48%).

A review of these SOCs demonstrated that the reported SAEs for GI disorders are consistent with the established safety profile of MMF. For example, adverse events including ulceration and hemorrhage are important identified risks of MMF, and the CellCept USPI warns prescribers about the risks of gastrointestinal bleeding requiring hospitalization, ulceration and perforations. In the case of surgical medical procedures, the reported SAES were identified post-operative complications of liver transplant surgery. Moreover, the higher proportion of SAEs reported within this SOC were generated by only six individual cases.

Conclusion: Thus, with the limitations of the database described in section 8.2.1, this reviewer concludes that no new safety signal emerged from review of SAEs in the company's safety database for pediatric liver transplant compared to adult liver transplant.

AEs / SAEs by SOC in Applicant safety database compared to pediatric kidney transplant:

As noted in section 8.2.1, 91 cases reporting 221 AEs for pediatric liver transplant recipients and 335 cases reporting 1141 AEs were retrieved for pediatric kidney transplant recipients from the Applicant's global safety database. Overall, the proportions of AEs reported in both pediatric liver transplant patients and pediatric kidney transplant patients were similar, except for a higher proportion of AEs for pediatric liver transplant patients in the SOCs Hepatobiliary disorders (4.98% vs 0.44%) and Gastrointestinal disorders (18.10% vs 13.85%).

For the SOC Hepatobiliary disorder, the AEs and SAEs such as jaundice, biliary obstruction, and chronic active hepatitis were expected complications post-liver transplant surgery or rejection. Thus, there were plausible alternative explanations for the AEs and SAEs identified.

For the SOC GI disorders, as described in the subsection above, the AEs and SAEs including ulceration and hemorrhage, are important identified risks of MMF, and the CellCept USPI warns prescribers about the risks requiring hospitalization.

The known limitations of post-marketing reporting and associated biases and a high percentage of duplicates reporting into the database also likely contributed to the larger difference in these proportional comparisons.

Conclusion: Thus, this reviewer concludes that no new safety signal emerged from a review of AEs/SAEs in the Applicant's safety database for pediatric liver transplant compared to pediatric kidney transplant.

Adequacy of the safety database:

There are no concerns with the adequacy or reliability of the company's safety database.

8.2.3. Applicant Conducted Clinical Studies Submitted in Support of Safety

The Applicant provided an estimated cumulative patient exposure to MMF in Applicant-sponsored interventional clinical trials where MMF was used as an investigational drug for any indication up to the database lock of May 2, 2021 for the latest Periodic Benefit-Risk Evaluation Report (PBRER). The estimated cumulative patient exposure to MMF for that time period was 16, 226 patients of which 451 patients were less than 18 years old. Further breakdown of pediatric age groups was not provided. Patients received MMF for approved (i.e., kidney transplant) and unapproved indications, as monotherapy, or combined with other medications.

Clinical Studies:
As noted in section 8.2.1, three studies provide safety data in pediatric patients: two studies in pediatric kidney transplant patients and one study in pediatric liver transplant patients.

Study MYC 2190, and the pivotal Study MYCS 2675 were submitted in support of approval for the pediatric kidney transplant indication and were completed in 1996 and 2000. A total of 140 pediatric patients have safety data available from these two studies. The Applicant submitted the final clinical study reports for Study MYC 2190 and Study MYCS 2675 with this sNDA.

Study MYC 2190:
A pilot pediatric study, MYC 2190, was a nonrandomized, multicenter, open-label study. Each patient was stratified to one of 3 age groups (less than 6 years; 6 years to less than 12 years; and 12 to 18 years;) and received 1 of 3 dose levels of oral MMF (15 mg/kg BID, 23 mg/kg BID, or 30 mg/kg BID) for the prevention of kidney allograft rejection. At study closure, most patients had received MMF for 1-2 years. Most patients chose to continue in the extension study at a dosage of 23 mg/kg BID until they had completed 3 years on MMF.

The dose selected from Study MYC 2190 was then subsequently tested in the pediatric pivotal Study MYCS 2675.

Study MYCS 2675:
Study MYCS 2675 was the pivotal study for the pediatric kidney transplant program as it provided the majority of the safety, PK, and efficacy data.

Study MYCS 2675 was a single-arm, open-label, safety, and PK study in 100 pediatric patients receiving a first or second kidney allograft. 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/m^2 b.i.d. (BSA) up to a maximum of 1 gram b.i.d., with cyclosporine and corticosteroids administered as per local center practice.

Safety conclusions from Study MYC 2190 and Study MYCS 2675:

All patients experienced at least one adverse event during the dose-ranging Study MYC 2190 and MYC 2190 V2. According to the medical officer's review of safety for NDA 50-722, SE5-007:

> "Qualitatively, the safety profile of MMF in pediatric renal transplant patients was similar to that observed in adult renal transplant patients. The youngest children experienced increased episodes of certain AEs (adverse events) including diarrhea, anemia, leukopenia and sepsis. However, these events either resolved spontaneously or with MMF dose modification. Furthermore, these events infrequently led to study discontinuation, had no long-term clinical sequelae and did not lead to death.
>
> Two cases of malignancy occurred in the pediatric group, both classified as lymphoma/lymphoproliferative disease (LPD). One case (Study MYCS 2675) occurred within 1 year (280 days) after starting MMF treatment; the other (Study MYCS 2190) occurred more than 3 years after starting MMF treatment. The resulting proportion of

lymphoma/LPD in the pediatric group after 1 year (1/140=0.7%) is very similar to that observed in the corresponding adult MMF-treated renal transplant population (2/336=0.6%). To date, no other types of malignancies have been reported in pediatric patients.

Based upon review of data submitted it appears that the safety and efficacy of CellCept in pediatric renal transplant recipients is similar to that of adult patients."

Pediatric Liver Transplant Study PA 16497:
This study was designed as an open-label, single-arm, two part study to assess the safety, tolerability, and PK of oral MMF in combination with CsA and CS in pediatric liver transplant recipients and was completed in 2005. Details of the study are discussed in section 6.2.1. Nine patients were enrolled between 9 months of age and 5 years with a median age of 17 months.

One AE was reported during the course of this study, pyrexia, and it was graded as mild.

Safety conclusions from Study MYC 2190, MYCS 2675 (pediatric kidney transplant), and PA 16497 (pediatric liver transplant):

The three clinical studies in pediatric patients indicate that the pediatric kidney and pediatric liver transplant population experienced similar AEs at comparable rates to their adult counterparts. It is important to note that the pediatric kidney transplant population did experience increased severity of GI systems, so dose titration of MMF may need to occur more cautiously.

8.2.4. Published Literature Studies Submitted in Support of Safety

Pediatric Heart Transplant
The publications submitted in support of safety of MMF in pediatric heart transplant include 12 publications, which evaluate a total of 456 pediatric patients. Two hundred and ninety-five (295) of these 456 patients were treated with MMF. The majority of the publications were retrospective but also include prospective studies and conference abstracts.

As noted above in section 8.2.1, Safety Review Approach, the age range of pediatric heart transplant patients varies widely in the studies. There is no study according to specific age groups (i.e., less than 2 years old). Nonetheless, a study by Groetzner et al 2005[8] does report the inclusion of a patient as young as 4 days old, the youngest age reported in the studies. However, subject level data regarding specific treatment, adverse events, and outcomes are not available.

Reported MMF doses vary from 250 mg/day (Groetzner et al 2005[8]) to a maximum of 2000 mg/day (Singh et al 2016[29]). Duration of treatment also varies and generally spans the study duration. The observation period ranged from 2 months up to 14 years in some retrospective studies.

Use of MMF in pediatric heart transplant patients less than 2 years old:

Six studies submitted in support of safety for pediatric heart transplant indication include patients under 2 years of age. The studies vary by design, objective, and endpoints. Age range of the participants was provided for most of the studies and spans from as young as 4 days old to 22 years old; however, specific details on outcomes and adverse events in patients less than 2 years old cannot be delineated from these studies as subject level data is not provided. Nonetheless, it is assumed that the authors' conclusions apply to all the age groups included in the studies.

For example, Groetzner et al 2005[8] conducted a single center retrospective study from 1988-2002 in 47 pediatric patients after heart transplantation with a mean age of 9.4 years but a range of 4 days to 18 years. In addition to the positive efficacy results specified in section 8.1.3 of this Unireview, the use of MMF was associated with an acceptable safety profile in this publication. They did not find an increase in infections or malignancy. Gastrointestinal side effects were noted in 12.1% of the patients (4/33) but were manageable with dose reduction or interruption.

In addition, Singh et al 2010[13] conducted a retrospective study in 55 pediatric patients after heart transplantation assessing a steroid avoidance protocol. The children ranged in age from 2 weeks to 22 years, with a median age of 7.1 years. Fifty of the 55 (50/55) patients made it to hospital discharge. Four of the five (4/5) deaths were in children less than one year old but were related to severe comorbidities and the severity of their condition, rather than to the immunosuppression regimen. For example, three of the four children who died were on extra-corporeal mechanical oxygenation (ECMO) prior to transplantation.

Overall, the studies including pediatric heart transplant patients under 2 years of age did not highlight increased or new safety concerns for this subgroup of the population.

Common AEs:

Among all age groups, common AEs reported include gastrointestinal (GI) disorders, infections and blood dyscrasias including leukopenia and anemia. Studies reporting on these three AEs will be described under each AE category.

Gastrointestinal (GI) Disorders:

Generally, gastrointestinal events, which include nausea, vomiting and diarrhea, were largely dose related and improved with dose reduction or interruption.

Three studies submitted by the Applicant reported severe GI side effects in 12%-20% of study patients requiring a switch to AZA or withdrawal of MMF. These studies were retrospective, assessed 22-47 pediatric heart transplant recipients on MMF as part of a combined regimen

(dose 250 mg/day-596 mg/m^2), and followed patients from 12 months to 14 years (Groetzner et al in 2005[8], Kis et al 2016[30], Siddiqi et al 2015[31]).

Infections:

Marshall et al. in 2013[11] conducted a retrospective, observational study in pediatric heart transplant patients comparing a CsA-AZA-steroid based protocol without induction (n=64) to a tac-MMF–based steroid-sparing protocol (n=39) with induction therapy between 2005 and 2010; patients in both groups experienced similar rates of bacterial, fungal, and viral infections (EBV infection, CMV infection) within the first 12 months after heart transplantation.

Jacobsen et al. in 2018[32] conducted a single arm, prospective, longitudinal cohort study of 28 pediatric heart transplant recipients who received maintenance therapy with tac, MMF, and oral steroids that were weaned by 6 months. Seven of 28 patients (7/28, 25%) had CMV DNA detection within first 12 weeks post-transplant. Also, Singh et al 2010[13] report CMV antigenemia in 11 out of 55 patients (11/55, 20%) and EBV viremia in 8 out of 55 patients (8/55, 14.5%) in their retrospective study of a cohort of pediatric heart transplant recipients on a steroid-avoidance protocol treated with tac and MMF.

Hingler et al 2013[33] conducted a prospective study comparing EBV load in pediatric heart transplant patients on a CsA plus MMF (n=38) regimen to patients on a CsA plus everolimus (EVE) regimen. Patients on CsA plus MMF (n=38) showed reduced EBV activity compared to patients on CsA plus Eve (# of patients unknown). Similarly, Schubert et al. 2008[34] in a prospective, single-center study observed that the EBV load was significantly reduced in patients on a CsA-MMF (740±382 copies/µg DNA) regimen compared to patients on a CsA–AZA (14,051± 4962 copies/µg DNA) and CsA only (891±623 copies/µg DNA) (p=.001) regimen.

Blood Dyscrasias:

Marshall et al in 2013[11] reported that anemia (51% vs 14%) and neutropenia (18% vs 5%) were more frequently seen in patients with on a tac plus MMF steroid-sparing group that did receive induction compared to the control group of CsA plus AZA and steroids that did not receive induction. However, the induction therapy of ATG and high dose methylprednisolone may have also contributed to the higher frequency of anemia and neutropenia, thereby, confounding the results. No difference in the frequency of thrombocytopenia was seen between the two groups (odds ratio: 1.1, 95% confidence interval: 0.3 to 4, p=0.9).

Summary of AEs:

According to the SRTR/OPTN data, MMF has largely replaced AZA as the anti-metabolite of choice in the majority of IS regimens for pediatric heart and liver transplant regimens. As stated earlier in the review, almost 90% of heart transplant IS regimens and almost 50% of liver transplant IS regimens included MMF as a part of there IS regimens in 2019. In support of this notable trend, Singh et al 2016[30] published a consensus statement on pharmacotherapies in

cardiac critical care reporting that MMF has replaced the use of AZA in most transplant centers. The authors also note that MMF is more specific for lymphocytes and results in fewer AEs.

Conclusion: In this Reviewer's assessment, the studies submitted in support of the pediatric heart transplant indication show that AEs due to MMF are largely dose-related including leukopenia, anemia, nausea, vomiting and diarrhea and can be managed with dose reduction, interruption, or discontinuation. These AEs are included in the CellCept USPI and no new safety signal has emerged from the literature review.

Pediatric Liver Transplant Studies:

Common AEs:

The common AEs reported in published studies of pediatric liver transplant patients also include gastrointestinal disorders, infections and blood dyscrasias. Each AE will be discussed below:

Gastrointestinal Disorders:

Chardot et al 2001,[18] Renz et al 1999,[35] and Aw et al 2008,[19] describe gastrointestinal symptoms of nausea, vomiting, and diarrhea developing in approximately 30% of patients in their studies. These studies were prospective (Chardot et al) and retrospective (Renz et al, Aw et al) and had varying numbers of patients. Dosing was also disparate from 10-43 mg/kg/day; however, GI tolerance was achieved by MMF dose reduction or dose interruption and resumption at a lower dose.

In addition, Sadiq et al in 2013,[36] presented a retrospective (part I) and prospective (part II) study assessing the incidence of MMF -induced diarrhea in 53 patients as an abstract at the 7th Congress on pediatric transplantation. Based on part I results, MMF dose was reduced for part II (dose not specified in abstract). Fewer patients reported moderate-severe diarrhea in part II compared to part I of the study (22/25, 85.7% vs 5/12, 41.6%).

Infections:

Leiskau et al 2018[25] compared infection risk in pediatric liver transplant recipients on MMF plus tac to retrospectively age and diagnosis matched patients on tac monotherapy and CsA plus steroid therapy; they did find a significantly higher risk of bacterial or mycotic infections (68.4%) compared to tac alone (31.6%, p=.04) and CsA plus steroid (57.6%, p=0.13) groups (exact number of patients who experienced these adverse events was not reported). However, EBV reactivation occurred less frequently in the MMF plus tac (47.4%) group compared to the tac alone (52.6%) and CsA plus steroid (84.2%) group (p=.05).

Weiner et al 2012,[37] in their retrospective chart review study, reported that 25% of pediatric liver transplant recipients developed EBV. These patients had received IL-2 receptor antibodies (dacilizumab) for induction, steroids and MMF, with delayed initiation of tac followed by steroid withdrawal by 6 months. Teisseyre et al 2006[26] found fewer EBV DNA copies, CMV infection, and hepatitis in pediatric liver transplant recipients on a tac plus MMF versus a tac plus steroid regimen. A subsequent prospective study by the same group in 2011 (Teisseyre et al[38]) showed

similar results with lower incidence of EBV infection in the tac plus MMF group compared to the tac plus steroids group at 1, 2, and 3 years after liver transplant (percentages not available, abstract).

Blood Dyscrasias:

Lightdale et al 1997[39] conducted a prospective, non-randomized study to evaluate the safety and effectiveness of MMF plus CsA and steroids compared to AZA plus CsA and steroids in 40 pediatric liver transplant patients. Forty-five percent (45%) of patients (9/20) in the MMF group versus 65% (13/20) in the AZA group experienced bone marrow suppression. Renz et al 1999[36] assessed the incidence of leukopenia with a protocol using MMF plus microemulsion-CsA (CNp) and steroids compared to AZA plus oil-based gel encapsulated CsA and steroids and anti-T cell antibody induction therapy (ACp). They found no difference in the incidence of leukopenia (i.e., definition as leukopenia requiring immunosuppression reduction or administration of granulocyte colony-stimulating factor). Incidences were 0 to 3 for CNp group vs 0 to 4 in the ACp group (p=.07).

Summary of AEs:

Blood dyscrasias and gastrointestinal complications including ulceration and perforations, are included in the warnings and precautions section of the CellCept label. Infections including opportunistic infections, are listed in the adverse reactions of the CellCept label. Chardot et al 2001[16] prospectively analyzed the use of MMF as a rescue therapy in pediatric liver transplant recipients. The authors note that 6 out of 19 (6/19, 32%) of patients dosed with MMF 12-43 mg/kg/day experienced mostly gastrointestinal and hematological side effects that resolved with cessation or dose reduction.

Conclusion: In this reviewer's assessment, the studies submitted in support of the pediatric liver transplant indication also show that AEs due to MMF are largely dose-related including leukopenia, anemia, nausea, vomiting and diarrhea and can be managed with dose reduction or interruption. These AEs are included in the CellCept USPI and no new safety signal has emerged from the literature review.

Serious Adverse Events

Pediatric Heart Transplant Studies**:**

PTLD:

PTLD is a serious adverse event that occurs in transplant recipients with varying rates according to organ transplant type. As described above, the rate of PTLD in pediatric patients is is 1-5% after kidney transplantation and 4-10% after heart or liver transplantation.[29]

A prospective, single-center, observational study by Schubert et al 2008,[35] measured EBV load and monitored immunosuppression therapy over 5 years. The patients were treated with an

MMF-CsA (N=17), CsA-AZA (N=11), or a CsA-Everolimus (N=9) regimen. Of those that developed PTLD, the majority of patients (67%) were on azathioprine prior to PTLD diagnosis and EBV load was significantly higher in patients on CsA-AZA compared to those on CsA-MMF. The authors concluded that patients on MMF were less likely to develop PTLD than patients on other immunosuppressive drugs.

Deaths:

The following studies submitted in support of the use of MMF for pediatric heart transplant reported deaths and possible causes of death. Singh et al 2010[13] reported 5 deaths out of 55 patients (5/55), which were related to early hospital mortality including multiple organ failure and not to rejection or immunosuppression. Groetzner et al 2005[8] report a perioperative mortality rate of 6% due to primary graft failure and a late mortality rate of 12% due to acute rejection, CMV pneumonia, and intracranial hemorrhage.

Pediatric Liver Transplant Studies:

PTLD:

Four of the 22 (4/22) publications submitted in support of safety for the pediatric liver transplant indication report on PTLD.

Chardot et al 2001[16] conducted a prospective study of the efficacy and safety of MMF in pediatric liver transplant patients. They report that 1 out of 19 (1/19, 5.2%) developed PTLD while on MMF and concluded that MMF does not increase the risk of PTLD. Aw et al 2008[19] conducted a retrospective study evaluating the long term outcome of MMF as rescue therapy for steroid resistant acute rejection in 26 pediatric liver transplant recipients. During a median follow up of 8.8 years, 5 of 26 were EBV seropositive, and 3 of those 5 developed PTLD (3/26, 11.5%).

Seo et al. in 2020[40] evaluated 142 pediatric liver transplant patients for EBV and monitored development of PTLD between 2006 and 2015. The number of pediatric patients on MMF was unknown. Of the total 142, 100 developed EBV in blood; 14 of these 100 developed PTLD. Two patients (2/100, 2%) died at 38 months and 16 months after diagnosis of PTLD.

Weiner et al 2012[38] completed a retrospective chart review of 187 pediatric liver transplant recipients for primary infection with EBV and PTLD. Forty-six patients (46/187, 24.5%) developed EBV positivity and 16 (16/187, 8.6%) patients developed PTLD.

Deaths:

In pediatric liver transplant recipients, the most common cause of death is post-operative complications. Seo et al 2020[41] report two deaths out of 142 (2/142, 1.4%) pediatric liver transplant recipients due to hepatic failure and acute respiratory distress syndrome in patients that had developed PTLD prior to their death. Post-operative complications are an important early cause of death in pediatric liver transplant recipients. Colombani et al 2000[41] conducted a retrospective study reviewing complications of liver transplant surgery and

immunosuppression. They reported on four early deaths (4/30, 13%) unrelated to immunosuppression (1 from primary non-function of allograft, 2 from sepsis, 1 from cardiac arrest and kidney failure) and 1 late death due to recurrent hepatitis.]

Summary of PTLD in pediatric heart and pediatric liver transplant recipients:

Though some of the reported rates of PTLD in the published studies are higher than the rates noted in the CellCept label (section 5.2, Post-transplant lymphoproliferative disorder (PTLD) developed in 0.4% to 1% of patients receiving CELLCEPT (2 g or 3 g) with other immunosuppressive agents in controlled clinical trials of kidney, heart and liver transplant patients), published studies indicate that children are at higher risk of developing PTLD for various reasons. These reasons include higher EBV seronegativity prior to transplantation and type of organ transplant. Mynarek et al 2013[29] note that EBV seronegativity carries a 4-fold increased risk of developing PTLD, organ recipients younger than 18 years carry a 2- to 4-fold higher risk of developing PTLD compared to adult transplant recipients, and pediatric heart and pediatric liver transplant recipients have a higher risk compared to pediatric kidney transplant recipients. In addition, many of these studies had a longer duration of follow up than in the pivotal clinical trials for the approved indications, which may be another reason higher rates of PTLD are seen. Despite these higher rates, the prognosis of PTLD is better for pediatric patients than adult patients, with 2-year survival noted to be between 70 and 80% in some studies.[29]

Summary of deaths in pediatric heart and pediatric liver transplant recipients:

The studies that report on deaths provide a qualitative description on common causes of death in the pediatric heart and liver patient populations. Also, given most of the studies were not designed to assess mortality and none were randomized controlled studies, it is difficult to attribute any of the deaths directly to MMF. Moreover, pediatric heart and liver transplant patients generally have multiple comorbidities and, in many cases, are critically ill prior to their transplant procedure; these patients are at even higher risk for mortality, particularly in the perioperative period. Nonetheless, the excellent 1 year patient and graft survival rates reported earlier in this review since the introduction of MMF into the IS regimen, indicate that MMF, in addition to other advancements in transplant surgery, has contributed to an improvement in mortality for these two vulnerable patient populations.

8.3. Statistical Issues

N/A

8.4. Conclusions and Recommendations

The current sNDA was submitted by the Applicant in response to an Agency request to add the pediatric heart and pediatric liver transplant indications to the CellCept package insert. The 2019 FDA guidance on Substantial Evidence of Effectiveness allows for " inclusion of pediatric use information in labeling without controlled clinical trials of the use in children. In such cases, a sponsor must provide other information to support pediatric use, and the Agency must

conclude that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit extrapolation from adult efficacy data to pediatric patients." [1]

The review strategy to support efficacy and the proposed dosing for both of the proposed indications is based on the following:

- Extrapolation of efficacy from adult kidney, heart, or liver transplant recipients and pediatric kidney transplant recipients.
- Established PK relationships among the approved populations derived from information in prior approval packages. See section 6, Clinical Pharmacology, for a thorough and detailed description of these relationships.
- For pediatric liver transplant recipients, support is also derived from a comparison of PK derived from Study PA 16497 with PK in the approved populations.
- For pediatric heart transplant recipients, supportive evidence is also provided from the literature.
- Data from SRTR/OPTN for heart and liver transplantation in the US provide context for interpretation of the available literature data.

The safety review is based on support from:

- Study MYC 2190 and Study MYCS 2675, the two pediatric kidney transplant studies reviewed under the approval package for the pediatric kidney transplant indication.
- PK Study, PA 16497, in pediatric liver transplant patients, which is the only new study submitted with this sNDA and not reviewed under a prior application.
- Safety data from publications describing the use of MMF in pediatric heart and pediatric liver transplant patients.
- Review of safety data from Applicant's post-marketing safety database.

The available clinical pharmacology data provide evidence suggesting that PK relationships across pediatric transplant populations mimics those observed across adult transplant populations; thus, support for extrapolation of efficacy and dosing from the approved populations to the proposed populations is reasonable. Second, the Applicant conducted clinical studies in adult kidney, heart, and liver transplant and pediatric kidney transplant patients demonstrate the efficacy of MMF in combination with CsA and CS in these populations. CsA is now known to interfere with the EHC of MMF, resulting in higher dosage requirements.

The proposed minimum dosage of 600 mg/m^2 BID has precedence as the approved dosage in pediatric kidney transplant patients. The proposed maximum dosage of 900 mg/m^2 BID matches the increase in the dosage recommended for adult heart transplant and liver transplant patients.

Concerns identified in this Unireview include limited clinical study and PK data in pediatric heart transplant patients less than 2 years old. Uncertainties such as possible ontogenetic changes in

IMPDH and deficiency in UGT, and high inter-individual variability in exposure with MMF dosing is also described in prior sections. Nonetheless, the available data in pediatric kidney transplant and pediatric liver transplant patients suggests that MPA exposure after MMF dosing remains approximately consistent across pediatric patients including in those younger than 2 years of age. Also, high inter-individual variability can be clinically managed with dose adjustments based on factors such as tolerability, concomitant medications, and laboratory parameters.

The widespread off label use of MMF with excellent outcomes noted in the SRTR/OPTN data and published studies from the past 20 years also support the clinical efficacy of MMF in the pediatric heart and pediatric liver transplant populations. These sources note excellent 1-year and 5-year graft survival and reasonable acute rejection rate outcomes.

In terms of safety, the most common AEs reported in the published literature for both indications include blood dyscrasias, gastrointestinal complications, and opportunistic infections, which are already included in the labeling either as adverse reactions or under warnings and precautions. The studies also show that AEs due to MMF are largely dose-related and can be managed with dose reduction or interruption.

In regard to SAEs, some of the reported rates of PTLD in the published studies are higher than the rates noted in the CellCept label. However, published studies indicate that children are at higher risk of developing PTLD for various reasons. These reasons include higher EBV seronegativity prior to transplantation and type of organ transplant. Specifically, pediatric heart and pediatric liver transplant recipients have a higher risk of PTLD compared to pediatric kidney transplant recipients. Despite these higher rates, the prognosis of PTLD is better for pediatric patients than adult patients, with 2-year survival noted to be between 70 and 80% in some studies.[29]

In regard to deaths reported in published studies, most of the studies were not designed to assess mortality and none were randomized controlled studies; therefore, it is difficult to attribute any of the reported deaths directly to MMF. Moreover, pediatric heart and liver transplant patients generally have multiple comorbidities and, in many cases, are critically ill prior to their transplant procedure; these patients are at even higher risk for mortality, particularly in the perioperative period. The excellent 1 year patient and graft survival rates reported earlier in this review since the introduction of MMF into the IS regimen, indicate that MMF, in addition to other advancements in transplant surgery, has contributed to an improvement in mortality for these two vulnerable patient populations

Overall, this clinical reviewer finds the evidence in support of efficacy, dosing, and safety for the use of MMF for the prophylaxis of organ rejection in the pediatric heart and pediatric liver transplant populations reasonable for approval. Based on internal discussions with all disciplines including Clinical Pharmacology and DPMH, this reviewer concurs that acceptable evidence has been submitted to align the dosing for the pediatric heart or liver transplant populations with that of the pediatric kidney transplant population. Thus, the proposed labeling for all patients including those aged 3 months to less than 2 years of age, will permit flexibility

in dosing at the clinician's discretion based on established clinical practice.

In conclusion, this Clinical reviewer considers the Applicant's proposal to extend the approved indication of CellCept for the prophylaxis of organ rejection in pediatric heart and pediatric liver transplant recipients acceptable and recommends approval.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee was not held for this efficacy sNDA.

10 Pediatrics

This efficacy sNDA was submitted to extend the indication of CellCept for use in the pediatric heart and liver transplant populations in response to an FDA request in 2018.

The adult liver transplant approval letter dated July 28, 2000 contained a PMC to to conduct an appropriate study or studies on the pharmacokinetics and safety of CellCept in very young (less than 12 years old) liver transplant recipients, especially infants (less than 3 years old with biliary atresia. The Applicant submitted the final clinical study report for PA 16497 on August 27, 2004 and the FDA issued a letter on October 5, 2009 releasing the Applicant of this PMC. PREA did not apply to the pediatric heart transplant indication as the adult heart transplant indication was approved prior to PREA's enactment. Please see section 3.2 of this Unireview for details of the interaction with the Applicant and the Agency and for the regulatory history prior to this submission.

DRTM consulted DPMH early in the review process. DPMH recommended DRTM present both indications to PeRC for review as they came under one efficacy supplement. The Division presented both indications at PeRC in February 2022. PeRC agreed on the Division's review strategy and the recommendation to grant a waiver for the birth to 3 month age group and for the IV formulation.

DPMH members including John Alexander, MD, MPH, Amy Taylor, MD, MHS, Shettara Walker, MD were present at the internal meetings. Concern arose that the data to support dosing for the pediatric heart transplant indication, particularly for patients under 2 years of age, was limited, as no clinical study or PK data was available in this population. The Applicant had relayed to the Division during pre-sNDA interactions that they had no intentions to complete any additional clinical studies. Firstly, as noted earlier in this Unireview, both indications are extremely rare with approximately 509 pediatric heart transplants performed in 2019 and less than 200 of those in patients under 2 years of age. Second, SRTR/OPTN data confirm that MMF has now become standard of care for the pediatric heart transplant population with more than

90% of transplant centers using MMF as part of their immunosuppressive regimen. Third, the excellent patient and graft survival rates of >90% at 1 year and >80% at 5-years across all age groups, as reported by SRTR/OPTN, also support the efficacy and safety of MMF in this population. In the face of these excellent outcomes, assessing MMF against an alternative regimen would raise ethical concerns.

Though other factors have contributed to the improvement in outcomes of pediatric heart and liver transplantation, the introduction of MMF in 1995 after the initial approval in the adult kidney transplant population is one of these important factors.

Thus, considering all of the points outlined above and the available data, this reviewer concurs with all the other disciplines and finds sufficient evidence in support of the efficacy and safety of MMF for the prophylaxis of organ rejection in the pediatric heart and liver transplant populations.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

11.1.1. Prescribing information

Table 15 presents a high-level summary of the labeling proposal and subsequent interactions between the Applicant and the Agency.

Table 15. High-Level Summary of labeling suggestions

Section	Labeling Discussions
Highlights, Indications and Usage	The Agency revised the indication to specify age group of pediatric patients: • *3 months of age and older*

Highlights, Dosage and Administration	The Agency did not agree with the Applicant's proposed (b) (4) (b) (4)
Highlights, Use in Specific Populations	• Removed the statement: (b) (4)
1 Indications and Dosage	• See above respective section under Highlights
2.2 Dosage and Administration	• See above respective section under Highlights
2.3 and 2.4 Dosage recommendations for Heart Transplant Patients and Liver Transplant Patients	• The Agency subdivided this section into Adults and Pediatrics to align with the kidney transplant section above • Included pediatric dosing with the specification for patients 3 months and older. The safety data in pediatric heart transplant patients <2 years is limited, therefore, the Agency leveraged data available in pediatric kidney transplant recipients and from published literature to extend the pediatric heart transplant indication down to 3 months of age. The goal was to increase access of MMF to this vulnerable patient population and allow clinicians' flexibility in management. • The Agency added the statement, "*The dose may be Individualized based on clinical assessment,"* to further allow for provider discretion in management of MMF dosing.
6.1 Clinical Trials Experience, Pediatrics	• The Applicant's proposed language was amended to specify that safety information for both indications is supported by data from publications and a PK study in pediatric liver transplant patients

7.1 Effect of Other Drugs on CellCept	• In Table 7 under "Drugs that Interfere with Enterohepatic Circulation," Cyclosporine A was added
8.4 Pediatric Use	• The statement, *"Safety and effectiveness have been established in pediatric patients 3 months and older for the prophylaxis of organ rejection of allogenic kidney, heart or liver transplants*," was moved (b) (4) to below the subsection title to include pediatric heart and liver transplants as well. • More specific language added to include the age group in which safety and efficacy have been established and the evidence which supports use in that age group.
12.3 Pharmacokinetics, Special Populations, Pediatric Patients	• The Agency included information indicating that pediatric liver transplant patients MPA AUC values were slightly lower than that for age and time post-transplant matched pediatric kidney patients. This is consistent with what is seen in the adult population; thus, pediatric liver transplant patients may need higher dosing to achieve the same exposure. • The Agency included a statement that MPA exposures are similar between adult kidney and heart transplant patients as well as between pediatric kidney and adult kidney transplant patients, thus, supporting extrapolation to pediatric heart transplant.
Sections 8.1 Pregnancy, 8.3 Females and Males of Reproductive Potential, 13.1 Nonclinical Toxicology	• The Agency requested the Applicant update multiples for the maximum recommended human doses (MRHDs) for pediatric patients with kidney, heart or liver transplants or provide the multiples based on plasma exposure as pediatric patients have relatively larger BSAs. • In response, the Sponsor provided updated multiples based on BSA. The Agency agreed with these multiples.
Medication Guide	• Revisions to patient labeling were made to align with the revised prescribing information, including the addition of the pediatric heart and liver transplant indication

Highlights of labeling changes from the above table are discussed below: (Recommended information to be added to selected sections of labeling is underlined. Information to be deleted has a strikethrough). Agency comments are italicized. These recommendations were discussed and agreed upon by all disciplines including DPMH and OPDP.

HIGHLIGHTS
Indication and Usage

CELLCEPT is an antimetabolite immunosuppressant indicated for the prophylaxis of organ rejection in adult and pediatric recipients 3 months of age and older of allogeneic kidney, heart or liver transplants, and should be used in combination with other immunosuppressants.

Agency comment: The age group in which the product is indicated should be included.

FULL PRESCRIBING INFORMATION

1. INDICATION AND USAGE

CELLCEPT [mycophenolate mofetil (MMF)] is indicated for the prophylaxis of organ rejection, in adult and pediatric recipients 3 months of age and older of allogeneic kidney [see Clinical Studies (14.1)], heart [see Clinical Studies (14.2)] or liver transplants [see Clinical Studies (14.3)], (b) (4) in combination with other immunosuppressants.

Agency comment: see above

2.3 Dosage (b) (4) Recommendations for Heart Transplant Patients

Pediatrics (3 months and older)

The recommended starting dosage (b) (4) of CELLCEPT oral suspension for pediatric heart transplant patients (b) (4) 3 months and older is 600 mg/m^2, administered twice daily (b) (4) (b) (4) If well tolerated, the dose can be increased to a maintenance dosage (b) (4) of 900 mg/m^2 twice daily (maximum total daily dose of 3 g or 15 mL of the oral suspension). The dose may be individualized based on clinical assessment. (b) (4)

Agency comment: Included pediatric dosing with the specification for patients 3 months and older. Though safety data in pediatric heart transplant patients less than 2 years is limited, the Agency leveraged data available in pediatric kidney transplant recipients and from published literature to extend the pediatric heart transplant indication down to 3 months of age.

The Agency did not agree with the Applicant's proposed (b) (4) *The agency decided to remove* (b) (4) *from the labeling.*

The goal was to increase access of MMF to this vulnerable patient population and allow clinicians flexibility in management.

2.4 Dosage (b) (4) Recommendations for Liver Transplant Patients

Pediatrics (3 months and older)

The recommended starting dosage (b) (4) of CELLCEPT oral suspension for pediatric (b) (4) transplant patients (b) (4) 3 months of age and older is 600 mg/m^2, administered twice daily (b) (4) If well tolerated, the dose can be increased to a maintenance dosage (b) (4) of 900 mg/m^2 twice daily (maximum total daily dose of 3 g or 15 mL of the oral suspension). The dose may be individualized based on clinical assessment.

(b) (4)

Agency comment: Same rationale as described above for pediatric heart transplant patients.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience

Pediatrics (b) (4)

(b) (4) Safety information (b) (4) in pediatric heart transplant or pediatric liver transplant patients treated with CELLCEPT is supported by an open-label study in pediatric liver transplant patients with long-term follow-up, and publications; (b) (4), the type and frequency of the reported adverse reactions (b) (4) are consistent with those (b) (4) observed in pediatric patients following renal transplant, and in adults.

Agency comment: The Applicant's proposed language was amended to specify that safety information for both indications is supported by data from publications and a PK study in pediatric liver transplant patients

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
Safety and effectiveness have been established in pediatric patients 3 months and older for the prophylaxis of organ rejection of allogenic kidney, heart, (b) (4) or liver transplants (b) (4)

Heart Transplant and Liver Transplant

Use of CELLCEPT in pediatric heart transplant and liver transplant patients is supported by adequate and well-controlled studies and pharmacokinetic data in adult heart transplant and liver transplant patients. Additional supportive data include pharmacokinetic data in pediatric kidney transplant and pediatric liver transplant patients (8 liver transplant patients, 9 months to 5 years of age, in an open-label, pharmacokinetic and safety study) and published evidence of clinical efficacy and safety in pediatric heart transplant and pediatric liver transplant patients [see Dosage and Administration (2.3 (b) (4), (b) (4) 2.4), Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.1)].

Agency comment: The statement, "Safety and effectiveness have been established in

pediatric patients 3 months and older for the prophylaxis of organ rejection of allogenic kidney, heart or liver transplants," was moved (b) (4) *to below the subsection title, 8.4 Pediatric Use, to include pediatric heart and liver transplants as well. More specific language to include the age group in which safety and efficacy have been established and the evidence which supports use in that age group.*

12.3 Pharmacokinetics

Pediatric Patients

A comparison of dose-normalized (to 600 mg/m^2) MPA AUC values in 12 pediatric kidney transplant patients less than 6 years of age (b) (4) at 9 months post-transplant with those values in (b) (4)7 pediatric liver transplant patients [median age 17 (b) (4) months (range: (b) (4)10 – 60 months)] and at (b) (4) 6 months and beyond post-transplant revealed that, at the same dose, there were on average 23% lower AUC values in the pediatric liver compared to pediatric kidney patients. This is consistent with the need of higher dosing (b) (4) in adult liver transplant patients compared to kidney transplant patients to achieve the same exposure.

In adult transplant patients administered the same dosage of CELLCEPT, there is similar MPA exposure among kidney transplant and heart transplant patients. Based on the established similarity in MPA exposure between pediatric kidney transplant and adult kidney transplant patients at their respective approved doses, it is expected that MPA exposure at the recommended dosage will be similar in pediatric heart transplant and adult heart transplant patients.

Agency comment: The Agency included information indicating that pediatric liver transplant patients MPA AUC values were slightly lower than that for age and time post-transplant matched pediatric kidney patients. This is consistent with what is seen in the adult population; thus, pediatric liver transplant patients may need higher dosing to achieve the same exposure. The Agency included a statement that MPA exposures are similar between adult kidney and heart transplant patients as well as between pediatric kidney and adult kidney transplant patients, thus, supporting extrapolation to pediatric heart transplant.

A tracked changes version of suggested labeling changes was conveyed to the Applicant on May 12, 2022. The Applicant submitted a response on May 16, 2022 accepting all changes except for one. Their only differing proposal was to strikethrough "long term follow up" under section 6.1 Clinical trials experience as the PK study only had 14-16 days follow up.

12 Risk Evaluation and Mitigation Strategies (REMS)

Section 8.1 of CellCept labeling discusses the increased risks of first trimester pregnancy loss and congenital malformations associated with exposure to MMF during pregnancy. Additional details are described in the current approved labeling.

The current sNDA would include women of childbearing potential as part of the intended population (pediatric heart and pediatric liver transplant patients aged 3 months and older). There is a REMS in place for CellCept (approved in September 2012) to address the increased risks of first trimester pregnancy loss and congenital malformations.

13 Postmarketing Requirements and Commitment

N/A.

14 Division Director (DHOT) Comments

N/A

15 Division Director (OCP) Comments

N/A

16 Division Director (OB) Comments

N/A

17 Division Director (Clinical) Comments

I concur with the team's assessment and recommendations that the evidence supported in this sNDA submission supports the approval of CellCept for use in pediatric heart and pediatric liver transplant recipients for the prophylaxis of organ rejection based on the following:

1. The mechanism of transplant organ rejection is similar across different organs, both in adults and children, and similar drug exposure in pediatric patients as in adults is expected to lead to the same therapeutic effect, permitting extrapolation from the

approved populations to pediatric heart transplant and pediatric liver transplant populations.

2. The Clinical Pharmacology review strategy to support the recommended dosing is based on established PK relationships across the approved adult kidney, heart, and liver transplant populations and the pediatric kidney transplant population.
3. For pediatric liver transplant patients, Study PA 16497 provides PK information that allows a comparison of exposures with PK in the approved populations. For pediatric heart transplant recipients, support for approval is also provided from the literature.
4. Additional supportive information in the form of patient and graft survival outcomes in pediatric heart and pediatric liver transplant recipients treated with MMF containing immunosuppressive regimens is provided from the SRTR databases. For both pediatric indications, support is also provided from the published literature.
5. A review of safety from the approved pediatric kidney transplant studies (MYC 2190, MYCS 2675), the pediatric liver transplant PK Study (PA 16497), published literature and the Applicant's post-marketing safety database did not raise new safety concerns. Additionally, already there is an approved REMS in place for mycophenolate products in order to mitigate the increased risks of first trimester pregnancy loss and congenital malformations associated with the use of MPA products .

I also agree with the clinical pharmacology review team in that I do not agree with the Applicant's proposal (b) (4)

18 Office Director (or designated signatory authority) Comments

N/A

19 Appendices

19.1. Financial Disclosure

Table 18. Description of studies and study dates

Study Number	Title	Phase	Study Dates
P180191 (Protocol MYC2190)	An Open-Label, Dose-Ranging, Pharmacokinetic, Safety and Tolerance Study of Oral Mycophenolate Mofetil in the Prevention of Rejection in Pediatric Renal Allograft Recipients	1	February 1994 - September 26, 1996
P180263 (Protocol MYCS2675)	An open-label, safety, tolerance, and pharmacokinetic study of oral mycophenolate mofetil suspension in the prophylaxis of rejection in pediatric renal allograft recipients.	1	July 16, 1997 – September 20, 1999
1019844 (Protocol PA16497)	A study of the safety, tolerability and pharmacokinetics of oral CellCept (mycophenolate mofetil, MMF) in pediatric liver transplant recipients on concomitant treatment with Cyclosporine and Corticosteroids	1	May 2, 2003 – January 20, 2005

(Source: Financial Disclosure Form, Module 1.2, NDA 50722/S-049, SDN 1066, submitted Nov. 22, 2021)
As submitted by the Applicant:

Study P180191 (Protocol MYC 2190) was completed in September 1996, which is prior to the effective date for the requirement for financial disclosure of clinical trials that were ongoing as of February 2, 1999.

Study P180263 (Protocol MYCS 2675) was originally submitted in sNDA 50722/S-007 on February 18, 2000. Financial disclosure information included in that submission (Vol 1, p. 10) states, “the primary pediatric Study MYCS 2675 has been excluded from the financial disclosure requirements because “no one investigator will make a significant contribution to the demonstration of safety” as agreed by FDA (FDA telefacsimile correspondence dated February 22, 1999).

Study 1019844 (Protocol PA 16497) is also a pharmacokinetic study which enrolled 9 pediatric patients, therefore a similar exclusion as agreed by FDA in February 1999 should apply.

19.2. Nonclinical Pharmacology/Toxicology

N/A

19.3. OCP Appendices (Technical documents supporting OCP recommendations)

Study PA 16497

The Applicant submitted results from Study PA 16497 completed in 2005: "A study of the safety, tolerability, and pharmacokinetics of oral CellCept (mycophenolate mofetil, MMF) in pediatric liver transplant recipients on concomitant treatment with cyclosporine and corticosteroids".

Primary Objective

This study was originally designed to consist of two parts. The primary objective of the first part of the study was to estimate the dose predicted to achieve an exposure of 58 mcg*h/mL in stable pediatric hepatic transplant patients. This dose was to be used in the second part of the study intended to confirm that the predicted dose from the first part yielded the desired MPA exposure. However, this study was terminated prematurely and only the first part of the study was completed.

Study Design

Part I of the study, the only part of the study conducted, was an uncontrolled, open-label, multicenter study. Nine pediatric transplant patients were enrolled and received MMF per center practice. All patients were on the same dose of MMF for at least 7 days prior to PK sampling. A complete clinical assessment was collected from all patients at Baseline. On Day 1, a 12-hour PK profile was collected for each patient. Adverse events were recorded throughout the study up to 14-16 days after PK sampling.

Inclusion and Exclusion Criteria

Study PA 16497 enrolled male or female patients between 9 months and 12 years of age. All patients were required to be recipients of a first liver allograft from cadaveric or living donors and must be at least 6 months post-transplant. Patients must have started MMF in the early post-transplant period (within 2 weeks of transplant) and receiving stable doses of MMF per center practice for at least 7 days prior to PK sampling. Patients were also required to be receiving stable doses of cyclosporine and corticosteroids per center practice.

Patients were not enrolled if they were pregnant or nursing, had undergoing dialysis within 2 weeks before PK sampling, had active systemic infections, active peptic ulcer disease, or had severe diarrhea or other gastrointestinal disorders which might interfere with their ability to absorb oral medication.

Patient Disposition and Demographics

Nine subjects aged 9 to 60 months (median age: 17 months) were enrolled, including four males and five females. Most patients were Caucasian (5 patients, 56%), while the remaining four were Black, Hispanic, Middle Eastern, and Asian. Five patients received transplants from living related donors, while the remaining four patients received cadaveric transplants. All

patients received concomitant immunosuppressants (cyclosporine). All other concomitant medications were administered to one patient and included fludrocortisone, omeprazole, and aspirin. The mean [range] values for weight, height, and body surface area were 10.97 [8.0, 14.5] kg, 77.67 [71.12, 86.36] cm, and 0.49 [0.40, 0.59] m^2, respectively.

One patient was prematurely withdrawn from the study as they had no venous access. PK samples could therefore not be collected. Patient demographics and MMF dosing for the eight patients who completed the study are summarized in the table below:

Table 19. Demographics of patients enrolled in Study PK 16497

Patient number	Gender	Race	Age (months)	Weight (kg)	Height (cm)	BSA (m^2)	MMF dose given (mg)	MMF dose/m^2	MMF dose/kg
(b) (6)	F	Caucasian	18	10.0	76.20	0.460	140	304	14.0
	M	Black	24	14.5	85.00	0.590	250	424	17.2
	M	Caucasian	17	10.5	73.00	0.460	170	370	16.2
	M	Other	9	8.1	71.12	0.400	90	225	11.1
	F	Other	60	11.6	86.36	0.530	125	236	10.8
	F	Caucasian	10	8.0	72.39	0.400	125	313	15.6
	F	Oriental	14	11.8	75.00	0.500	100	200	8.47
	F	Caucasian	15	10.5	76.00	0.470	100	213	9.52
Mean (±SD)			20.9 (16.5)	10.6 (2.11)	76.9 (5.72)	0.476 (0.064)	138 (52.2)	285 (81.1)	12.9 (3.32)
Median			16.0	10.5	75.5	0.465	125	270	12.6

BSA=body surface area; F=female; M=male; MMF=mycophenolate mofetil; SD=standard deviation.

(*Source: Summary of Clinical Pharmacology, page 52, module 2.7.2, NDA 50722/S-049, SDN 1050, submitted Sept. 10, 2021*)

PK Sample Collection

Sampling times for PK profiles were dependent on age. A total of 9 blood samples were collected in patients 24 months of age and older at pre-dose, and post-dose at hours 0.5, 0.75, 1, 1.5, 2, 4, 8, and 12. A total of 5 blood samples were collected in patients less than 24 months of age at pre-dose, and post-dose at hours 0.75, 2, 4, and 12. Patients were required to fast from 2 hours pre-dose until 2 hours post-dose and antacids were not permitted on the PK sampling day.

PK Analysis

All randomized and replaced patients adherent to the protocol were included in the PK analysis. PK samples were analyzed using a validated HPLC/UV method. Further details of the bioanalytical method are provided in a subsequent section.

PK parameters, including T_{max}, C_{max}, and AUC_{0-12} for MPA and MPAG, were calculated using a non-compartmental method and summarized descriptively. The primary PK parameter was MPA AUC_{0-12} normalized to dose and body surface area. Individual AUC values were divided by the ratio of the individual dose in units of mg over body surface area measurements in units of m^2. Raw MPAG plasma concentrations were adjusted to MPA Equivalent Units by multiplying each concentration by the ratio of the molecular weights of MPA and MPAG. MPAG C_{max} and AUC were expressed as MPA equivalents. The C_{max} and AUC_{0-12} for MPA and raw and molecular-weight adjusted MPAG were normalized to a dose of 600 mg/m^2 and 1.5 grams.

The dose predicted to achieve an AUC of 58 mcg*h/mL was estimated based on the AUC values determined at the doses subjects were receiving and the PK linearity of MPA. Per the approved labeling for CellCept, MPA AUC increases in a dose-proportional fashion in kidney transplant patients receiving multiple oral doses of MMF up to a daily dose of 3 g (1.5 g twice daily).

PK Data Adjustments and Exclusions

One plasma sample was missing from patient (b) (6) at the 0.75 hour time point. One sample collected from patient (b) (6) at the 0.75 hour time point produced no result with insufficient material for re-extraction and was therefore considered missing data. Concentrations that were below the limit of quantitation at the end of the concentration-time profile were considered missing data, including the following:

- Patient (b) (6) MPA at 12 hours
  - The MPA AUC calculated for this subjects was an AUC_{last}, for which evaluable samples were available up to 8 hours post-dose.
- Patient (b) (6), MPAG at 12 hours
  - MPAG AUC was not calculable as AUC_{last} was > 5% different from AUC_{tau}
- Patient (b) (6), MPAG at 12 hours
  - MPAG AUC was not calculable as there were no measureable plasma concentrations available after 4 hours.

Most PK profiles only contained two data points on the terminal part of the log-linear concentration-time curve as most patients (6/8) were younger than 24 months of age and therefore only had 5 samples collected over 12 hours. In a few cases, C_{max} was used as one of those two data points. A comparison between AUC_{0-12} (AUC_{tau}) and AUC_{last} was performed and a < 1% difference was observed on each occasion, except where noted.

Validation and Bioanalytical Report Review

During the initial NDA submission, no bioanalytical report was provided for Study PA 16497. An information request was sent to the Applicant on Oct. 8, 2021 to request a bioanalytical report

as well as a validation report if the method used was not the same as that used in previously submitted studies. The Applicant provided a response, including the requested reports on Oct. 19, 2021.

In the Applicant's response, it was indicated that some errors were made in the original study report for Study PA 16497. It was clarified that the assay used to quantify mycophenolic acid (MPA) and its glucuronide metabolite (MPAG) was a high-performance liquid chromatography/ultraviolet (HPLC/UV) method. In addition, the LLOQ for MPAG was not 1.00 µg/mL, but 4 µg/mL.

The Applicant also confirmed that the same isocratic HPLC/UV method has been used for quantitative determination of MPA and MPAG in samples from studies PA 16497, MYCS 2675, and MYCS 2190. The latter two studies were conducted in pediatric kidney transplant recipients and previously reviewed by the Agency. The Applicant has also indicated that small adjustments to the methods were made in different laboratories to optimize local performance although each analytical laboratory has re-validated the method. The following table provides an overview of the analytical sites, method characteristics and performance of the method, including limits of quantification, precision, and accuracy.

Table 20. Overview of CellCept Bioanalytical Methods for MPA and MPAG

Table 1: Overview of CellCept Bioanalytical Methods for MPA and MPAG[*]

Study ID		PA16497	MYCS2675	MYCS2190
Bioanalytical Source Document		Bioanalytical Report [1] (Supplemental Report to Roche Clinical Study Report P-1019844)	Roche Report P-180263 [2]	Syntex Research Report, Method IAR-B-1006 [3, 4]
Analytical Site		(b) (4)		Roche (Syntex Dept. of Bioanalysis) (some parts at (b) (4) (b) (4)
Sample Work-up		SPE C18	Protein precipitation; no SPE	SPE C18
Internal Standard	MPG	RS-60461	RS-60461	RS-60461
	MPAG	Phenolphthalein glucuronic acid	Phenolphthalein glucuronic acid	Phenolphthalein glucuronic acid
Chromatographic Conditions				
HPLC Column		C18 Hypersil BDS 5µ 150x4.6 mm	C18	C18 Novapak 4µ 150x3.9 mm (Waters) (or equivalent)
Mobile Phase	MPA	ACN: aq. H_3PO_4 0.05 % 39:61 (v:v)	ACN: aq. H_3PO_4 0.043 % 44:56 (v:v)	ACN: MeOH: aq. H_3PO_4 0.05 % 25:20:55
	MPAG	ACN: aq. H_3PO_4 0.05 % 21:79 (v:v)	ACN: aq. H_3PO_4 0.043 % 22:78 (v:v)	ACN: aq. H_3PO_4 0.05 % 21:79 (v:v)
Detection Method		UV	UV 254 nm	UV 254 nm
Limit of Quantification	MPA	0.100 µg/mL	0.100 µg/mL	0.100 µg/mL[†]
	MPAG	4.00 µg/mL	4.00 µg/mL	4.00 µg/mL[2]
Precision (CV%)	MPA	4.2-8.8%	2.86-7.75%	2.4-7.7%
	MPAG	4.7-5.8%	3.00-6.55%	0.29-4.1%
Accuracy	MPA	95.4-100%	96.3-100%	96.6-105%
	MPAG	91.7-107%	98.5-102%	98.0-105%

[*] SPE Solid Phase Extraction; MeOH Methanol; ACN Acetonitrile; H_3PO_4 Phosphoric acid; aq. aqueous
[†] Numbers taken from P-180191

(*Source: Response to Information Request page 3, Module 1.11.3, NDA 050722/S-049, SDN 1057, submitted Oct. 19, 2021*)

Validation Report IAR-B1006: An HPLC Method for the Simultaneous Determination of Mycophenolic Acid and its Glucuronide Conjugate in Plasma

This validation report describes the general method used to detect MPA and MPAG in plasma, but the parameters most closely resemble those used for Study MYCS2190 conducted in pediatric kidney transplant recipients. Across studies, some parameters of the method are expected to differ as the analytical sites varied. This includes the mobile phases used for analysis and determined precision and accuracy. The Applicant has indicated that small adjustments were made to methods across analytical sites to optimize local performance and each site has re-validated the method.

The bioanalytical method uses a workup method in which plasma samples are acidified and purified using C-18 solid phase extraction. The eluent containing analytes and internal standards are then run through high-performance liquid chromatography (HPLC) using a mobile phase that consists of either a 25:20:55 mixture of acetonitrile, methanol, and 0.05% aqueous phosphoric acid for MPA, or a 21:79 mixture of acetonitrile and 0.05% aqueous phosphoric acid for MPAG. Sample detection for MPA and MPAG was performed via UV at 254 nm.

The limit of quantification of the method is 0.400 µg of MPA or MPAG per mL of plasma. The linear range is 0.200 to 10.0 µg/aliquot of plasma for MPA and 0.200 to 100 µg/aliquot of plasma for MPAG. For MPA, the inter- and intra-assay coefficients of variation (CV) were < 8% over the entire range. For MPAG, inter- and intra-assay CV were < 5% and ≤ 13%, respectively, over the entire range.

Relative recovery for MPA and MPAG ranged from 94 to 109% and 94 to 105%, respectively. MPA and MPAG were stable in whole blood and plasma at room temperature for at least 4 hours and at 1-4 °C for at least 8 hours. Both MPA and MPAG were stable in plasma when stored in a freezer at -20 °C for at least 6 months. Both compounds are stable following three freeze-thaw cycles. Specificity of the method was also assessed to evaluate possible interference from endogenous components in human plasma, co-administered compounds, and parent drug. No interference from internal standards was also observed. It was also noted that parent drug does not degrade to MPA or MPAG during the analytical procedure.

This method appears adequately validated for analysis of MPA and MPAG in human plasma.

Bioanalytical Report 1019844: Analytical Determination of Mycophenolic Acid (MPA) and its Glucuronide (MPAG) in Human Plasma Samples from Clinical Protocol PA16497

A total of 47 plasma samples were collected during Study PA16497. The method used to analyze samples from Study PA16497 is very similar to the method described above in

validation report IAR-B1006, but used a different HPLC column and mobile phase for elution of MPA.

The limits of quantification for MPA and MPAG was approximately 0.100 µg/mL and 4.00 µg/mL, respectively. As applied to samples analyzed for Study PA16497, the accuracy ranged from 95.4 to 100% for MPA and 91.7 to 107% for MPAG. Across all samples for MPA and MPAG, the inter-assay CV% for quality control samples was ≤ 8.8%. It is noted that since different batches of quality control samples were used, the inter-assay precision was calculated using the accuracy results instead of back-calculated concentrations from quality control samples.

Incurred sample reanalysis was performed on approximately 10% of samples (n = 5). All five samples were analyzed separately for MPA and for MPAG. For both MPA and MPAG, three out of five samples reanalyzed were within 20% of the mean. Of the remaining two samples, reanalysis of one sample was not within 20% of the mean. For the remaining sample, CV% was not calculated as the original and re-analyzed values were below the limit of quantitation and therefore no specific values were reported.

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20 **Appendix**

CellCept labeling as negotiated with the applicant and likely to be final:

39 Pages of draft labeling have been withheld in full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HUSEYIN E VELIDEDEOGLU
06/06/2022 01:33:02 PM
Cellcept sNDA Unireview (Peds Efficacy Supplement for heart and liver tx)