Multidisciplinary Review

Table 1. Application Information

Application type	NDA
Application number(s)	204410/S-029
Priority or standard	Priority
Submit date(s)	August 30, 2024
Received date(s)	August 30, 2024
PDUFA goal date	February 28, 2025
Division/office	DCN/OCHEN
Review completion date	February 26, 2025
Established/proper name	Macitentan
(Proposed) proprietary name	OPSUMIT
Pharmacologic class	Endothelin receptor antagonist
Applicant	Janssen Research and Development
Dosage form(s)/formulation(s)	Tablets, for oral use
Dosing regimen	10 mg once daily
Applicant-proposed indication(s)/ population(s)	No new indication proposed
SNOMED CT code for proposed indication disease term(s)[1]	11399002 |Pulmonary hypertensive arterial disease (disorder)|
Regulatory action	Approval
Approved dosage (if applicable)	10 mg once daily
Approved indication(s)/ population(s) (if applicable)	For the treatment of pulmonary arterial hypertension (PAH, WHO Group I) in adults to reduce the risks of disease progression and hospitalization for PAH.
SNOMED CT code for approved indication disease term(s)[1]	11399002 |Pulmonary hypertensive arterial disease (disorder)|

[1]*For internal tracking purposes only.*

Abbreviations: DCN, Division of Cardiology and Nephrology; NDA, New Drug Application; OCHEN, Office of cardiology, hematology, endocrinology and nephrology; PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

Table 2. Reviewers of Multidisciplinary Assessment

Role	Name(s)
OCP reviewer(s)	Chongwoo Yu, PhD, Yun Wang PhD
OCP team leader(s)	Yoo Jin (Elly) Moon, PharmD, Jiang Liu, PhD
Clinical reviewer	Christine Garnett, PharmD
Biometrics reviewer	Ja-An (Joanne) Lin, PhD
Biometrics team leader(s)	James Travis, PhD, Jennifer Clark, PhD
Division director (OB)	Mark Rothmann, PhD
Division director (DCN) and Signatory	Aliza Thompson, MD, MS

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	alkaline phosphatase
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BA	bioavailability
BE	bioequivalence
BID	twice daily
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit-Risk Framework
BSA	body surface area
CDER	Center for Drug Evaluation and Research
CDTL	cross-discipline team leader
CEC	clinical event committee
CFR	Code of Federal Regulations
CHD	congenital heart disease
CI	confidence interval
C_{max}	maximum plasma concentration
CR	complete response
CRF	case report form
CRO	clinician-reported outcome
CSR	clinical study report
DMC	data monitoring committee
DPMH	Division of Pediatric and Maternal Health

eCTD	electronic common technical document
EFD	embryo-fetal development
EMA	European Medical Agency
EOCP	end of core period
EOS	end of study
ERA	endothelin receptor antagonist
ET	endothelin
FAS	full analysis set
FC	functional class
FDA	Food and Drug Administration
FU	follow up
GCP	good clinical practice
GLP	good laboratory practice
GRMP	good review management practice
hPAH	hereditary pulmonary arterial hypertension
HR	hazard ratio
ICH	International Council for Harmonisation
IND	investigational new drug
iPAH	idiopathic pulmonary arterial hypertension
IV	intravenous
KM	Kaplan-Meier
LLN	lower limit of normal
LOCF	last observation carried forward
LS	least square
LVEDP	left ventricular end diastolic pressure
LVEI	left ventricular ejection index
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed models for repeat measures
MVPA	moderate to vigorous physical activity
NA	not applicable
NDA	new drug application

NME	new molecular entity
NT-proBNP	N-terminal pro–B-type natriuretic peptide
OB	Office of Biostatistics
OCP	Office of Clinical Pharmacology
OCMQ	OND custom medical query
OND	Office of New Drugs
OR	odds ratio
OSI	Office of Scientific Investigations
PAP	pulmonary arterial pressure
PAH	pulmonary arterial hypertension
PAWP	pulmonary arterial wedge pressure
PD	pharmacodynamic
PDE-5i	phosphodiesterase type 5 inhibitor
PI	Prescribing Information
PIP	pediatric investigational plan
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert
PPSR	proposed pediatric study request
PREA	Pediatric Research Equity Act
PT	preferred term
PVR	Pulmonary vascular resistance
QD	once daily
QoL	quality of life
RD	risk difference
REMS	risk evaluation and mitigation strategy
RHC	right heart catheterization
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SC	subcutaneous

SE	standard error
SOC	system organ class
SoC	standard of care
SP	study phase
TAPSE	tricuspid annular plane systolic excursion
TBIL	total bilirubin
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TQT	thorough QT
ULN	upper limit of normal
USPI	U.S. Prescribing Information
WHO	World Health Organization
WR	written request

I. Executive Summary

1. Summary of Regulatory Action

OPSUMIT (macitentan) is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to reduce the risks of disease progression and hospitalization for PAH in adults. On August 30, 2024, Janssen Research & Development submitted a supplemental NDA for macitentan to (1) provide the clinical trial data from the TOMORROW study, which was conducted under a Written Request (WR); (2) propose labeling within the pediatric section with the results of the pediatric clinical trial; and (3) provide evidence that the Applicant fairly responded to the WR. Of note, the Applicant has not proposed an update to the Indications and Usage Section of the label because "neither safety nor efficacy has been established from the results of the pivotal study, AC-055-312 (TOMORROW)." This review focuses on the results of the TOMORROW study as relates to the proposed labeling changes. The Pediatric Exclusivity Board's recommendations regarding Pediatric Exclusivity (PE) for macitentan are addressed in a separate memorandum.

In brief, the efficacy of macitentan in pediatric patients aged 1 month to less than 18 years was evaluated in the TOMORROW study. TOMORROW was initially designed as a multicenter, open-label, randomized, parallel-group, group-sequential, event-driven study to assess the efficacy, safety, and PK of macitentan versus standard of care (SoC) in children with PAH. The prespecified primary efficacy endpoint of the trial was the time to the first of the following Clinical Event Committee (CEC)-confirmed disease progression events: death (all causes), atrial septostomy or Potts' anastomosis, registration on lung transplant list, hospitalization due to worsening PAH or clinical worsening of PAH. However, because recruitment into the study and event accrual were slower than anticipated, the Applicant changed the primary endpoint to a pharmacokinetic (PK) endpoint and all efficacy endpoints were changed to secondary endpoints without alpha adjustment for multiplicity. As discussed in the body of this review, compared to SoC, there was no significant effect on time to CEC-confirmed disease progression events; however, only 45 (21 in macitentan vs. 24 in SoC) of the planned 187 disease progression events had occurred by the end of the study. As such, the failure to detect an effect on the endpoint is not interpretable. Analyses of other endpoints are also challenging to interpret, even ignoring multiplicity issues, given the uncertainty in estimates (as reflected by wide confidence intervals around estimates that do not exclude a null effect), missing data, and/or questions about the clinical significance of some of the endpoints.

In their supplemental NDA, the Applicant proposed updates to Section 8.4. describing the results of the TOMORROW study. The review team has revised the proposed text to include a more succinct description of the pediatric study results. The description notes that although the trial did not demonstrate a clinical benefit of macitentan compared with standard of care in the treatment of PAH, it cannot be ruled out that a trial with a different design would demonstrate a clinical benefit in this patient population. The Applicant agrees with the proposed edits to the label; hence the supplement will be approved.

2. Benefit–Risk Assessment

2.1. Benefit–Risk Framework

Table 3. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	PAH (World Health Organization Group 1) is a rare, serious, and progressive disease. It is characterized by increased pulmonary vascular resistance, increased pulmonary artery pressure, and right ventricular dysfunction, which leads to right heart failure, morbidity, and mortality. Both adults and children have the same hemodynamic definition of PAH. Data from the Netherlands in 2011 showed an annual incidence and point prevalence (per million children) of 0.7 and 4.4 for iPAH and 2.2 and 15.6 for PAH due to CHD (van Loon RL, 2011). Pediatric PAH shares common features of adult disease. Both populations have vascular and endothelial dysfunction, and similar histopathology. Children have a greater predominance of iPAH, hPAH and PAH due to CHD (Barst, 2011). Children with PAH appear to have more similarities in disease characteristics to adults with PAH than differences.	PAH in children is a rare, serious, and progressive disease with significant morbidity and mortality. The disease in children is similar to the adult disease such that pediatric development programs for drugs shown to be effective in adults can rely on pediatric extrapolation approaches.
Current treatment options	To date, two agents have been approved in the US for the treatment of PAH in pediatric patients. Bosentan is approved for pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance which is expected to result in an improvement in exercise ability. Sildenafil is approved for children and adolescents, 1−17 years, to improve exercise ability and, in pediatric patients too young to perform standardized exercise testing, pulmonary hemodynamics thought to underlie improvements in exercise. PAH-specific drugs approved in adults are extensively used off-label in children based on recommendations in clinical guidelines and consensus statements (Ivy, 2024; Hansmann, 2019; Abman, 2015).	Pediatric PAH remains an area of unmet medical need. Only two agents are approved for pediatric PAH and no agents are approved for children under 1 year of age. Therapeutic algorithms in children are largely based on expert opinion and evidence-based adult studies.
Benefit	The efficacy of macitentan in pediatric patients was evaluated in the TOMORROW study. TOMORROW was initially designed as a multicenter, open-label, randomized, parallel-group, group-sequential, event-driven study to assess the efficacy, safety, and PK of macitentan versus SoC in children with PAH. However, because of difficulty enrolling participants into the study and low accrual of disease progression events, the Applicant changed the primary endpoint to a	Overall, the data from the TOMORROW study do not support or refute the effectiveness of macitentan in pediatric patients with PAH.

	PK endpoint and all efficacy endpoints were changed to secondary endpoints without alpha adjustment for multiplicity. TOMORROW enrolled 148 pediatric subjects ≥2 years and 9 subjects <2 years. Subjects had idiopathic/heritable PAH (52%), WHO functional class II/III (75%) and taking PDE-5i monotherapy (51%). Of note, ERA use prescribed as SOC before randomization could continue in the SOC arm, but the proportion of subjects on ERAs was to be capped.[1] At baseline, approximately 45% of subjects were on background treatment of PDE-5i + ERA or ERA monotherapy in the SOC arm. PK Results: Simulations from the Applicant's population pharmacokinetics model showed a similar distribution of AUCu,combo,ss values between pediatric weight groups (for participants ≥2 years) and adults, with lower exposures in participants <2 years. The results for secondary efficacy endpoints were as follows: • Time to First Disease Progression Event[2]: Compared to SoC, there was no significant effect on time to disease progression. Only 45 (21 in macitentan vs. 24 in SoC) of the planned 187 clinical worsening events had occurred by the end of the study, resulting in a stratified HR of 0.84 and a 95% CI that crossed one (95% CI: 0.47, 1.52). • WHO Function Classification: Compared to SoC, there was no significant difference between the treatment arms in the proportion of subjects with WHO FC I or II at Weeks 12 and 24. While the estimates of the stratified OR numerically favored the macitentan arm, the CIs were wide and did not exclude the null hypothesis (stratified OR of 4.6 with 95% CI: 0.8, 25.90 at Week 12 and stratified OR of 6.4 with 95% CI: 1.1, 37.2 at Week 24). • NT-proBNP: Compared to SoC, there was no significant difference between treatment arms in the reduction in NT-proBNP at Weeks 12 and 24. Based on an MMRM model, the reduction from baseline in NT-proBNP was numerically greater in the macitentan arm; however, the 95% CIs of the mean ratio crossed one and over 12% of data were missing in both arms. The clinical significance of this endpoint is also unclear since macitentan's effect on NT-proBNP levels in the phase 3 trial conducted in adults did not appear to predict macitentan's effect on clinical	• Although the TOMORROW study did not demonstrate a significant effect on time to disease progression event, the study was underpowered to do so. As such, the failure to detect such an effect is not interpretable. • Analyses of other endpoints are also challenging to interpret, even ignoring multiplicity issues, given the uncertainty in estimates (as reflected by wide confidence intervals around estimates that do not exclude a null effect), missing data, and/or questions about the clinical significance of some of the endpoints. • It is unclear whether a trial with a different design would demonstrate a clinical benefit in this patient population. In principle, use of another ERA in the SOC control arm in TOMORROW would have made it more difficult to detect a difference between arms.

[1] According to the protocol, the proportion of subjects with ERA treatment, as a component of the planned SoC, was to be limited to a maximum of 40% of the overall number of subjects. During discussions of the design of the development program, the Division voiced concern about permitting the use of an ERA in the SoC arm and specifically voiced concern that a failed trial that compares macitentan, an ERA, with standard of care that includes another ERA would be uninterpretable. The Applicant contended that prohibiting such use would making it challenging to enroll patients into the trial, given the widespread use of ERAs in the pediatric population, and thus implemented a cap on enrollment.

[2] Terminology reflects terminology used by the Applicant. DCN has been standardizing the terminology used to describe clinical endpoints in labeling for PAH drugs. Current practice is to refer to this endpoint as "clinical worsening events."

	outcomes[3]. Therefore, the data obtained in adults do not support use of this biomarker to extrapolate the efficacy findings seen in adults treated with macitentan to children. • Other Secondary Endpoints: Exploratory analyses of endpoints derived from accelerometry, echocardiography and QoL measured by Pediatric Quality of Life Inventory™ did not suggest an obvious or consistent effect on these endpoints.	
Risk and risk management	Risks of macitentan based on the pharmacologic class and studies in animals and in adults with PAH include embryo-fetal toxicity, hepatotoxicity, fluid retention, decreases in hemoglobin, pulmonary edema with pulmonary veno-occlusive disease and decreased sperm counts. Embryo-fetal toxicity is currently managed through a REMS. Other adverse reactions are managed through labeling. In subjects ≥2 years, the total exposure to macitentan was 253 person-years with a median duration of exposure of 168 weeks. In subjects <2 years, median duration of macitentan treatment was 37 weeks. Adverse events (identified by narrow OCMQ query) occurring ≥10% more in the macitentan arm compared to SoC included nasopharyngitis, viral infection, bacterial infection and anemia. Increased infections are not a known risk of macitentan or other ERAs and this imbalance likely reflects a chance finding. Decreases in hemoglobin are a known risk of ERAs, including macitentan. Approximately 15% of subjects in the macitentan arm as compared to 3% of subjects in the SoC arm had at least 1 anemia event. Anemia SAEs occurred in 2 subjects in the macitentan arm; both were severe, and one led to treatment withdrawal. 13 deaths occurred in TOMORROW: 7 deaths in the macitentan arm and 6 deaths in the SoC arm; all these deaths occurred in subjects ≥2 years. The CEC-confirmed that 6 deaths in the macitentan arm and 4 deaths in the SoC arm were due to PAH disease progression. AEs with fatal outcome included COVID-19 and hypoxic-ischemic encephalopathy. A review of serious AEs and discontinuations due to AEs did not indicate a concerning pattern in the macitentan arm.	The safety profile in TOMORROW is consistent with the known safety profile in adults with PAH.

Abbreviations: AE, adverse events; AUCu,combo, sum of macitentan and aprocitentan AUC0-24h,ss weighted by their unbound fraction and by their proportion of in vitro potency; BSA, body surface area; CEC, clinical events committee; CHD, congenital heart disease; CI, confidence interval; ERA, endothelin receptor antagonist; FC; functional classification; HR, hazard ratio; MMRM, mixed model for repeat measures; OCMQ, OND custom medical query; OR, odds ratio; hPAH; hereditary PAH; iPAH, idiopathic PAH; PK, pharmacokinetics; nOCMQ, narrow OCMQ; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PDE-5, phosphodiesterase type 5 inhibitor; PVR, pulmonary vascular resistance; RD, risk difference; REMS, risk evaluation and mitigation strategy; SAE, serious adverse event; SoC, standard of care; QoL, quality of life; TAPSE, tricuspid annular plane systolic excursion.

[3] In the biomarker analysis using the subset of all randomized patients to macitentan 10 mg or placebo (n=330) in the SERAPHIN study, the percentage of the treatment effect explained by the change in NT-proBNP at 6 months was around 16%, which was considered too low to provide confidence in the use of NT-proBNP as a bridging biomarker. NT-proBNP was quantified by the Biomedica method (mass units fmol /mL) which could have altered the observed treatment effect (Type C Meeting minutes, 08/17/2022).

2.2. Conclusions Regarding Benefit-Risk

The efficacy of macitentan in pediatric patients aged 1 month to less than 18 years with pulmonary arterial hypertension (PAH) was evaluated in the TOMORROW study, but the results were inconclusive. The study design was modified from an event-driven protocol to a pharmacokinetic study with a fixed completion date of February 28, 2024, due to enrollment challenges and slow accrual of disease progression events. A total of 157 participants were enrolled, including 148 patients ≥2 years of age and 9 patients <2 years of age. By the study completion date, only 45 of the pre-specified 187 disease progression events had occurred. Consequently, the amended study design was not adequately powered to assess the treatment effect on disease progression events. Analyses of other efficacy endpoints are also challenging to interpret, even ignoring multiplicity issues, given the uncertainty in estimates (as reflected by wide confidence intervals around estimates that do not exclude a null effect), missing data, and/or questions about the clinical significance of some of the endpoints. In summary, the data from the TOMORROW study neither support nor refute the efficacy of macitentan in pediatric patients.

Macitentan is associated with known risks, including embryo-fetal toxicity, hepatotoxicity, fluid retention, decreases in hemoglobin, pulmonary edema in patients with pulmonary veno-occlusive disease, and decreased sperm counts. The adverse events (AEs) and serious adverse events (SAEs) observed in the TOMORROW study were consistent with the established safety profile of macitentan. No additional adverse reactions were identified in the pediatric population.

Based on the available data, the TOMORROW study did not demonstrate a favorable benefit-risk profile for macitentan in pediatric patients with PAH.

In consultation with the Division of Pediatrics and Maternal Health, the review team recommends updating section 8.4 of the OPSUMIT label to state that the clinical benefit of macitentan was not demonstrated in the TOMORROW study. The Pediatric Review Committee agreed with this approach during a meeting held on February 4, 2025. Thus, the review team recommends the following description of the pediatric study in section 8.4 Pediatric Use:

> OPSUMIT was evaluated in 148 pediatric patients 2 to 17 years of age with PAH in a single open-label, randomized trial with an extension period in which all patients received treatment. The trial did not demonstrate a clinical benefit of OPSUMIT compared with standard of care in the treatment of PAH. It cannot be ruled out that a trial with a different design would demonstrate a clinical benefit in this patient population. Adverse reactions observed in the trial were similar in nature to those reported in clinical trials in adults.

II. Interdisciplinary Assessment

3. Introduction

Janssen Research & Development (herein referred to as the Applicant) submitted a supplemental NDA to (1) provide pediatric clinical trial data in accordance with the Written Request (WR) under Best Pharmaceuticals for Children Act (BPCA); (2) propose labeling within the pediatric section with the results of the pediatric clinical trial; and (3) provide evidence that the Applicant responded to the WR. The Applicant is not seeking marketing approval of macitentan for the treatment of pulmonary arterial hypertension (PAH) in pediatric patients aged 1 month to less than 18 years because neither efficacy nor safety was demonstrated in the phase 3 study AC-055-312 (TOMORROW).

PAH is a rare cardiopulmonary disorder in which progressive remodeling of the pulmonary vasculature is largely responsible for the rise in pulmonary artery pressure and pulmonary vascular resistance which results in right heart failure. Children with PAH may have either idiopathic or hereditary PAH or PAH associated with different types of congenital heart disease (CHD). Data from the Netherlands in 2011 showed an annual incidence and point prevalence (per million children) of 0.7 and 4.4 for idiopathic PAH and 2.2 and 15.6 for PAH-CHD (van Loon RL, 2011).

PAH in children is an area of unmet medical need. In the US, bosentan and sildenafil are indicated for the treatment of pediatrics with PAH (WHO Group 1). Bosentan is an ERA and was shown to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability in children 3 to 17 years. Bosentan can cause hepatotoxicity and requires close monitoring of liver function. Sildenafil is a phosphodiesterase type 5 inhibitor (PDE-5i) and was shown to improve exercise ability in children 1 to 17 years. Treatment strategies in children are based on experience with off-label use of drugs approved in adults. For children with lower-risk PAH, treatment guidelines developed by the American Heart Association and American Thoracic Society recommend off-label treatment with oral PAH-targeted therapy (Class I; Level of Evidence B) including either a phosphodiesterase type 5 inhibitor (PDE-5i), such as sildenafil or tadalafil, or an endothelin receptor antagonist (ERA), such as bosentan or ambrisentan (Abman, 2016). Current treatment guidelines also recommend the initiation of combination therapies in children with higher risk, such as a combination PDE-5i + ERA (Ivy 2024).

TOMORROW was initially designed as a multicenter, open-label, randomized, parallel-group, group-sequential, event-driven study to assess the efficacy, safety, and pharmacokinetics (PK) of macitentan versus standard of care (SoC) in children with PAH. The primary efficacy endpoint was time to the first disease progression event.[4] However, the Applicant changed the study to a PK study because of difficulty enrolling participants into the study (**Table 4**). The Division disagreed with the Applicant's decision to amend the primary endpoint (b) (4) (b) (4)

Development for macitentan was conducted under IND 77258. On January 22, 2016, the Applicant submitted a Proposed Pediatric Study Request (PPSR) to NDA 204410 to evaluate macitentan in

[4] Different terminology have been used to describe the endpoint in PAH development programs. Current Division practice is to refer to this endpoint as "clinical worsening events" in product labeling.

children aged 1 month to less than 18 years with PAH in the TOMORROW trial. The Agency issued a pediatric WR for this study on April 13, 2016 with a final pediatric study report due on April 12, 2021. The Applicant conducted the TOMORROW study under a Pediatric Investigational Plan with EMA. On May 3, 2018, due to a patent extension for OPSUMIT (December 5, 2025), the Applicant submitted a request to amend the due date for the final pediatric study report to October 5, 2024. On April 23, 2020, the WR was amended and the due date for the final pediatric study report was changed to October 5, 2024. A detailed regulatory history is presented in section 12.

3.1. Review Issue List

As previously noted, the Applicant submitted this supplement to (1) provide pediatric clinical trial data in accordance with the WR under BPCA; (2) propose labeling within the pediatric section with the results of the pediatric clinical trial; and (3) provide evidence that the Applicant responded to the WR. This review focuses on the results of the TOMORROW trial as relates to the proposed labeling changes.

3.2. Approach to the Clinical Review

Table 4 provides an overview of the TOMORROW trial conducted to support the benefit and risk assessment in pediatric patients with PAH.

Table 4. Clinical Studies/Trials Submitted in Support of Efficacy and Safety Determinations[1] for Macitentan

Study	NCT	Design	Regimen/ Schedule/ Route	Endpoints	Treatment Duration/ Follow-Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
TOMORROW/ AC-055-312 Amendment 8, Version 9	02932410	A multicenter, open-label, randomized study with single-arm extension period to assess the pharmacokinetics, safety, and efficacy of macitentan versus standard of care in 157 children with PAH. Children < 2 years will be assigned as a cohort to the macitentan group without randomization.	Macitentan was administered after dispersion of tablet(s) in water even to subjects who can swallow tablets. The dose is adjusted to the subject's age (for those < 2 years) or to the subject's body weight (for those ≥ 2 years) at treatment assignment	**Primary:** Pharmacokinetics **Secondary:** • Safety and tolerability • Efficacy o Disease progression events[5] o Hospitalization for PAH o Death due to PAH o All-cause death o WHO FC o NT-proBNP o Physical activity o TAPSE o LVEI o PedsQL	Study duration for each individual subject will be based on their time of enrollment. All subjects are planned to remain in the study until the database lock in 2024	Macitentan: 73 subjects ≥ 2 years 9 subjects <2 years SoC: 75 subjects ≥ 2 years	Male and female pediatric participants with PAH who were ≥1 month to <18years.	51 centers in 18 countries (Australia, Brazil, China, Colombia, Spain, France, Hungary, Israel, Republic of Korea, Mexico, Philippines, Poland, Portugal, Russian Federation, Thailand, Ukraine, United States of America, and Viet Nam)

Source: Reviewer

[1] Includes all submitted clinical 'trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.

[2] If no randomization, then replace with "Actual Enrolled."

Abbreviations: BID, twice daily; DB, double-blind; LTE, long-term extension; MC, multicenter; N, number of subjects; NCT, national clinical trial; OL, open-label; PG, parallel group; R, randomized; h, hour; d, day; wk, week(s); mo, month(s); y, year(s)

[5] Different terminology have been used to describe the endpoint in PAH development programs. Current Division practice is to refer to this endpoint as "clinical worsening events" in product labeling.

4. Patient Experience Data

The study included a quality of life assessment, the PedsQL™ 4.0 Generic Core Scales Short Form (SF15), as a secondary endpoint. For the youngest age category (toddlers) the questionnaire exists only for parent/caregiver (i.e., Parent Report). For all other age categories separate questionnaires exist for parent/caregiver and for subjects (i.e., Child report) and address the same items. For the cohort of children < 2 years, this questionnaire is not available. Although there appeared to be an initial numerical increase in the SF15 score in the macitentan arm that was not seen in the SOC arm, there did not appear to be a difference between arms at later time points (see Figure 22 in Appendix). Patient and observer-reported outcomes from open-label studies can also be challenging to interpret given knowledge of treatment assignment.

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☑	Patient-reported outcome	See discussion above table.
☑	Observer-reported outcome	See discussion above table.
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Endothelin (ET)-1 and its receptors (ET A and ET B) mediate a variety of deleterious effects, such as vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation. In disease conditions such as PAH, the local ET system is upregulated and is involved in vascular hypertrophy and in organ damage.

Macitentan is an endothelin receptor antagonist that inhibits the binding of ET-1 to both ET A and ET B receptors. Macitentan displays high affinity and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells. One of the metabolites of macitentan is also pharmacologically active at the ET receptors and is estimated to be about 20% as potent as the parent drug in vitro. The clinical impact of dual endothelin blockage is unknown.

See Pharmacology/Toxicology review for NDA 204410 by Dr. William Link (08/26/2013) in DARRTs.

5.2. Clinical Pharmacology/Pharmacokinetics

5.2.1. Study AC-055-312 (TOMORROW): Pharmacokinetics (PK), safety, and efficacy study

As previously noted, Study AC-055-312 was a multicenter, open label, randomized, Phase 3 study with a single-arm extension period in pediatric participants with PAH aged ≥ 1 month to < 18 years. Participants in the macitentan arm received macitentan dispersible tablets (i.e., pediatric final market image [FMI] formulation [i.e., 1.0 and 2.5 mg dispersible tablet]) QD). Daily doses for participants aged ≥ 2 years ranged from 3.5 to 10 mg, depending on the body weight category (**Table 6**). Body weight for potential dose adjustment was measured every 12 weeks at scheduled study visits. Participants aged < 6 months and participants aged ≥ 6 months but < 2 years received fixed daily doses of 1 and 2.5 mg, respectively. The dose for participants aged < 2 years was selected based on modeling and simulation of the PK data from pediatric participants aged ≥ 2 years and adults.

Table 6. Proposed Dosing Scheme by Age and Body Weight, as Used in the Pediatric Studies

Age and Body Weight Categories	Daily Dose (mg), Oral	Tablets (FMI)
≥1 month and <6 months	1	1 tablet 1.0 mg
≥6 months and <2 years	2.5	1 tablet 2.5 mg
≥2 years, ≥10 kg and <15 kg	3.5	1 tablet 1.0 mg+1 tablet 2.5 mg
≥2 years, ≥15 kg and <25 kg	5	2 tablets 2.5 mg
≥2 years, ≥25 kg and <50 kg	7.5	3 tablets 2.5 mg
≥2 years, ≥50 kg	10 (consistent with the adult daily dose)	4 tablets 2.5 mg

FMI=final market image

Source: Table 1, Module 2.7.2

The revised primary endpoint was evaluation of trough (i.e., pre-dose) plasma concentrations of macitentan and its active metabolite, aprocitentan at steady state. For all participants who received macitentan, single trough samples (i.e., pre-dose) were taken at Week 12 for participants aged ≥ 2 years and at Weeks 4 and 8 for participants aged < 2 years.

In addition to the protocol-mandated PK trough assessment, an optional PK substudy was performed. For participants aged ≥ 2 years, steady-state PK samples were collected after the same macitentan dose had been administered for at least 10 continuous days. A total of 7 blood samples were drawn at the following timepoints: pre-dose, and 1, 2, 4, 8, 12, and 24 (i.e., before taking the next macitentan dose) hours post-dose. These PK profiles were analyzed for the following age categories: 2 to < 6 years, 6 to < 12 years, and 12 to < 18 years, and additionally, by body weight group. For participants aged < 2 years, PK samples were collected after the first dose (i.e., Day 1). A total of 3 PK samples were collected at 2, 5, and 24 (i.e., before the macitentan dose on the next day) hours post-dose.

Participants Aged ≥2 Years:
Trough plasma concentrations at steady-state (i.e., Week 12) in participants ≥ 2 years are shown in **Table 7** (overall and by body weight), and **Table 8** (by age group).

Table 7. Trough (Pre-Dose) Plasma Concentrations of Macitentan and Aprocitentan at Week 12 (Steady-State) for Participants ≥ 2 Years - by Body Weight and Overall

TPK01:	Trough (Pre-Dose) Plasma Concentrations of Macitentan and Aprocitentan at Week 12 (Steady State) for Subjects ≥ 2 Years Old - by Body Weight and Overall; PK Set 1 (Study AC-055-312)	
	Macitentan JNJ67896062 (ng/mL)	Aprocitentan JNJ68212820 (ng/mL)
Analysis set: PK Set 1	47	47
Weight subgroup: ≥ 10 kg and < 15 kg		
N	6	6
Mean (SD)	150.133 (67.5742)	1165.000 (390.7628)
SE of Mean	27.5870	159.5283
95% CI for Mean	79.219; 221.048	754.920; 1575.080
Coefficient of Variation (%)	45.0	33.5
Geometric Mean	136.004	1110.915
Median	144.500	1100.000
Range	(58.80; 246.00)	(748.00; 1660.00)
Weight subgroup: ≥ 15 kg and < 25 kg		
N	12	12
Mean (SD)	153.892 (108.3185)	859.333 (217.2926)
SE of Mean	31.2689	62.7270
95% CI for Mean	85.069; 222.714	721.272; 997.394
Coefficient of Variation (%)	70.4	25.3
Geometric Mean	128.096	834.386
Median	102.500	823.000
Range	(57.40; 402.00)	(522.00; 1210.00)
Weight subgroup: ≥ 25 kg and < 50 kg		
N	14	14
Mean (SD)	200.975 (151.6511)	980.857 (391.3308)
SE of Mean	40.5305	104.5876
95% CI for Mean	113.414; 288.536	754.909; 1206.805
Coefficient of Variation (%)	75.5	39.9
Geometric Mean	143.072	900.035
Median	172.500	1024.000
Range	(6.75; 581.00)	(370.00; 1530.00)
Weight subgroup: ≥ 50 kg		
N	15	15
Mean (SD)	208.067 (92.4246)	1011.267 (288.3632)
SE of Mean	23.8639	74.4551
95% CI for Mean	156.884; 259.250	851.576; 1170.957
Coefficient of Variation (%)	44.4	28.5
Geometric Mean	176.247	960.324
Median	226.000	1060.000
Range	(19.20; 334.00)	(339.00; 1450.00)
Overall		
N	47	47
Mean (SD)	184.727 (114.2953)	983.043 (324.1086)
SE of Mean	16.6717	47.2761
95% CI for Mean	151.168; 218.285	887.881; 1078.204
Coefficient of Variation (%)	61.9	33.0
Geometric Mean	147.703	925.804
Median	158.000	986.000
Range	(6.75; 581.00)	(339.00; 1660.00)

Key: CI=Confidence interval; SD=Standard deviation; SE=Standard error.

Source: Table 16, Study AC-055-312 CSR

Table 8. Trough (Pre-Dose) Plasma Concentrations of Macitentan and Aprocitentan at Week 12 (Steady-State) for Participants ≥ 2 Years Old - by Age; PK Set 1 (Study AC-055-312)

TPK02:	Trough (Pre-Dose) Plasma Concentrations of Macitentan and Aprocitentan at Week 12 (Steady State) for Subjects ≥ 2 Years Old - by Age; PK Set 1 (Study AC-055-312)	
	Macitentan JNJ67896062 (ng/mL)	Aprocitentan JNJ68212820 (ng/mL)
Analysis set: PK Set 1	47	47
Age subgroup: ≥ 2 - < 6 years		
N	9	9
Mean (SD)	159.767 (84.5424)	1063.333 (376.4173)
SE of Mean	28.1808	125.4724
95% CI for Mean	94.782; 224.752	773.993; 1352.673
Coefficient of Variation (%)	52.9	35.4
Geometric Mean	141.258	1007.225
Median	132.000	1090.000
Range	(58.80; 325.00)	(674.00; 1660.00)
Age subgroup: ≥ 6 - < 12 years		
	Macitentan JNJ67896062 (ng/mL)	Aprocitentan JNJ68212820 (ng/mL)
N	19	19
Mean (SD)	184.792 (148.2530)	957.211 (335.0858)
SE of Mean	34.0116	76.8740
95% CI for Mean	113.336; 256.248	795.704; 1118.717
Coefficient of Variation (%)	80.2	35.0
Geometric Mean	131.729	898.013
Median	119.000	910.000
Range	(6.75; 581.00)	(370.00; 1530.00)
Age subgroup: ≥ 12 - < 18 years		
N	19	19
Mean (SD)	196.484 (88.1549)	970.842 (298.5151)
SE of Mean	20.2241	68.4841
95% CI for Mean	153.995; 238.973	826.962; 1114.722
Coefficient of Variation (%)	44.9	30.7
Geometric Mean	169.151	917.096
Median	192.000	1050.000
Range	(19.20; 334.00)	(339.00; 1450.00)

Key: CI=Confidence interval; SD=Standard deviation; SE=Standard error.

Source: Table 17, Study AC-055-312 CSR

Key PK parameters of macitentan and aprocitentan are summarized by age group in **Table 9** and by body weight group in **Table 10**.

Table 9. Steady-state PK Parameters of Macitentan and Aprocitentan in Pediatric Participants (≥ 2 Years) With PAH, Stratified by Age Group, After Administration of 3.5,

5.0, 7.5, or 10 mg Macitentan Once Daily, Based on Body Weight (Study AC-055-312, PK Substudy), Compared to Adults With PAH

Age Group	n	C_{max} (ng/mL)	t_{max} (h)	AUC_{τ} (ng×h/mL)
			Macitentan	
≥2 and <6 years	4	406 (156)	5.97 (2.02 - 8.00)	5,346 (1,885)
≥6 and <12 years	9	343 (104)	8.40 (3.98 - 24.07)	5,898 (1,942)
≥12 and <18 years	13	388 (126)	4.13 (1.00 - 8.20)	6,435 (1,970)
Adults (10 mg QD)	20	430 (159)	6.50 (5.0 - 14.0)	7,200 (3,203)
			Aprocitentan	
≥2 and <6 years	4	1,306 (730)	0.00 (0.00 - 24.00)	24,053 (11,618)
≥6 and <12 years	9	1,081 (360)	8.05 (0.00 - 23.95)	21,934 (6,531)
≥12 and <18 years	13	1,045 (355)	2.00 (0.00 - 24.00)	21,708 (7,210)
Adults (10 mg QD)	20	1,036 (301)	6.50 (5.0 - 24.0)	21,234 (6,476)

PAH=pulmonary arterial hypertension; PK=pharmacokinetic; QD=once daily; SD=standard deviation.
Note: Arithmetic means (SD) are given for all PK parameters except t_{max}, where median (range) is given.
Note: Adult PAH patients: source study AC-055-303, Day 2.

Source: Table 4, Study AC-055-312 CSR

Table 10. Steady-state PK Parameters of Macitentan and Aprocitentan in Pediatric Participants (≥ 2 Years) With PAH, Stratified by Weight Group After Administration of 3.5, 5.0, 7.5, or 10 mg Macitentan Once Daily, Based on Body Weight (Study AC-055-312, PK Substudy), Compared to Adults With PAH

Body Weight Group	n	C_{max} (ng/mL)	t_{max} (h)	AUC_{τ} (ng×h/mL)
			Macitentan	
≥10 kg and <15 kg (3.5 mg QD)	3	477 (75.5)	8.00 (2.02 - 8.00)	6,217 (885)
≥15 kg and <25 kg (5.0 mg QD)	5	323 (81.8)	8.08 (3.93 - 11.98)	5,565 (1,631)
≥25 kg and <50 kg (7.5 mg QD)	9	356 (122)	8.00 (3.98 - 24.07)	6,066 (2,268)
≥50 kg (10 mg QD)	9	389 (141)	4.05 (1.00 - 8.20)	6,339 (2,125)
Adults (10 mg QD)	20	430 (159)	6.50 (5.0 - 14.0)	7,200 (3,203)
			Aprocitentan	
≥10 kg and <15 kg (3.5 mg QD)	3	1,519 (726)	0.00 (0.00 - 24.00)	27,763 (10,947)
≥15 kg and <25 kg (5.0 mg QD)	5	997 (283)	8.05 (0.00 - 23.95)	20,508 (6,134)
≥25 kg and <50 kg (7.5 mg QD)	9	1,015 (402)	0.00 (0.00 - 12.20)	20,925 (7,165)
≥50 kg (10 mg QD)	9	1,096 (363)	7.98 (0.00 - 24.00)	22,407 (7,619)
Adults (10 mg QD)	20	1,036 (301)	6.50 (5.0 - 24.0)	21,234 (6,476)

PAH=pulmonary arterial hypertension; PK=pharmacokinetic; QD=once daily; SD=standard deviation.
Note: Arithmetic means (SD) are given for all PK parameters except t_{max}, where median (range) is given.
Note: Adult PAH patients: source study AC-055-303, Day 2.

Source: Table 5, Study AC-055-312 CSR

Out of 29 subjects in the PK substudy, only 26 subjects were included in tables above. For Subjects (b) (6) the administered dose was not in line with the body weight at the time of PK substudy visit. They received 5.0 mg instead of 7.5 mg. Data from these subjects were included in the plasma concentration and PK parameter tables but excluded from descriptive statistics and graphical analyses. In addition, for Subject (b) (6) the 2, 4, and 12 hr post-dose PK samples were not taken or not available. Consequently, PK parameters Tmax, Cmax, and AUC for this subject was excluded from descriptive statistics as the missing samples could have overlapped with Cmax.

Participants Aged < 2 Years:

The plasma concentration data were available for 9 participants aged < 2 years (age range: 1.2 to 1.9 years). Trough (pre-dose) plasma concentrations of macitentan and its active metabolite, aprocitentan at steady-state (i.e., Week 4) for 9 participants are summarized in **Table 11**.

Table 11. Trough (Pre-Dose) Plasma Concentrations of Macitentan and Aprocitentan for Participants < 2 Years; PK3 Analysis Set (Study AC-055-312)

Subject ID	Visit	Macitentan JNJ67896062 concentration (ng/mL)	Aprocitentan JNJ68212820 concentration (ng/mL)
(b) (6)	WEEK 4	166	1020
	WEEK 8	39.8	505
	WEEK 4	57.8	766
	WEEK 8	40.7	784
	UNSCHEDULED	260	1610
	WEEK 8	274	1460
	WEEK 4	BQL<(1.00)	19.5
	WEEK 8	42.5	851
	WEEK 4	186	863
	WEEK 4	87.3	954
	WEEK 4	BQL<(1.00)	10.3
	WEEK 8	171	131
	WEEK 4	39.3	713
	WEEK 4	106	558
	WEEK 8	139	660

Key: BQL=below quantification level

Source: Table 17, Study AC-055-312 CSR

The macitentan and aprocitentan concentrations collected over 24 hours (after the first dose of macitentan, 2, 5, and 24 hours post-dose) are summarized in **Table 12** for 8 of the 9 participants aged < 2 years. The reason for missing data of 1 subject is unknown.

Table 12. Macitentan and Aprocitentan Concentrations Over 24 Hours (Following First Macitentan Administration) for Participants Aged < 2 Years (Study AC-055-312)

	Macitentan (ng/mL)	Aprocitentan (ng/mL)
2 Hours Post-Dose		
N	8	8
Mean (SD)	68.488 (64.0632)	11.253 (12.5401)
SE of Mean	22.6498	4.4336
95% CI for Mean	14.929; 122.046	0.769; 21.736
CV (%)	93.5	111.4
Geometric Mean	41.799	7.165
Median	54.250	7.960
Range	(11.20; 177.00)	(0.00; 36.60)
5 Hours Post-Dose		
N	8	8
Mean (SD)	169.538 (118.7360)	46.713 (35.7820)
SE of Mean	41.9795	12.6508
95% CI for Mean	70.272; 268.803	16.798; 76.627
CV (%)	70.0	76.6
Geometric Mean	145.791	36.759
Median	125.500	31.250
Range	(90.40; 440.00)	(13.80; 106.00)
24 Hours Post-Dose		
N	8	8
Mean (SD)	96.263 (50.1974)	207.500 (67.6461)
SE of Mean	17.7475	23.9165
95% CI for Mean	54.296; 138.229	150.946; 264.054
CV (%)	52.1	32.6
Geometric Mean	86.094	198.273
Median	86.950	215.500
Range	(42.00; 195.00)	(130.00; 335.00)

CI=confidence interval; CV=coefficient of variation; SD=standard deviation; SE=standard error.
Note: Data cutoff: up to individual EOCP date.
Note: Concentrations reported as below the limit of quantification are imputed with 0.

Source: Table 5, Module 2.7.2

It should be noted that there were no pass/fail criteria set for the PK assessment of this study.

5.2.2. Study AC-055-121: Relative Bioavailability (BA) Study (Initial Phase 3 Formulation [CSF] vs. OPSUMIT)

This study was conducted to assess the relative BA of the initial Phase 3 dispersible tablet formulation (i.e., clinical service formulation [CSF]) with the OPSUMIT film-coated tablet that is approved for adults.

This was a single-center, open-label, randomized, 2-treatment, single-dose, 2-period crossover study. A total of 12 healthy Caucasian male adult participants were randomly assigned to 1 of 2 treatment sequences (i.e., A-B or B-A) and all 12 subjects have completed the study. Treatments A and B

each consisted of a single 10 mg dose of macitentan using 2 different formulations:

- Treatment A (Reference): 10 mg dose given as 1 OPSUMIT film-coated tablet (G001) with 240 mL of water
- Treatment B (Test): 10 mg dose given as 2 dispersible tablets of 5 mg for pediatric use (CSF; G013). The pediatric formulation was suspended in a tablespoon of water, approximately 10-15 mL taken from the 240 mL, for 1 min. Subjects were administered the suspended study drug, followed by drinking the remaining water.

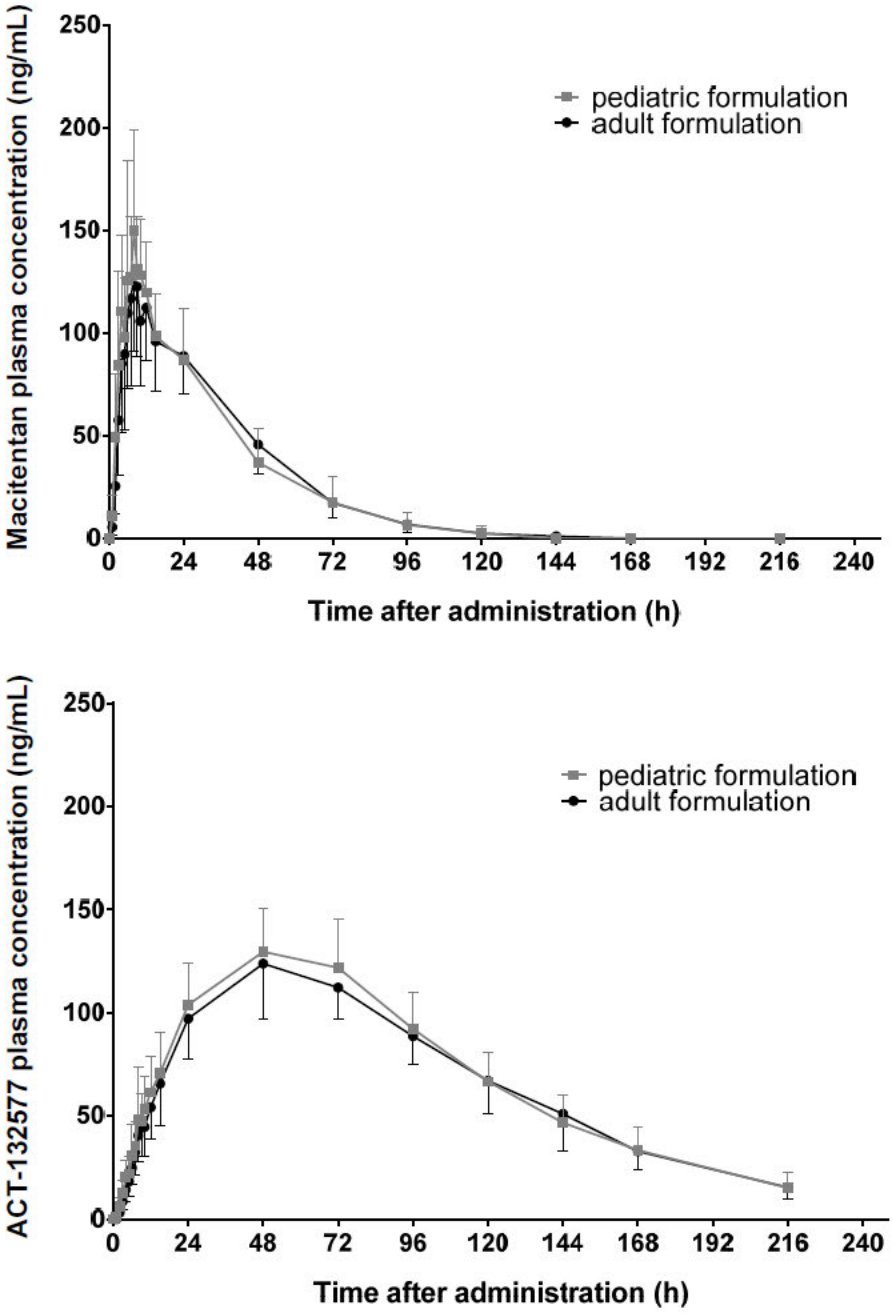
Treatments were administered under fasting conditions. Each observation period lasted 216 hours, with treatment periods separated by a washout period of 11-14 days between Day 10 of the first treatment period and Day 1 of the second treatment period.

Blood samples for measurement of macitentan and its active metabolite, aprocitentan concentrations were taken at prespecified time points (i.e., at pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 24, 48, 72, 96, 120, 144, 168, and 216 hours post-dose).

There were no major protocol deviations, concomitant medication issues, or violations of the inclusion and exclusion criteria that led to exclusion of subjects from any analysis set.

Mean macitentan and aprocitentan (ACT-132577) plasma concentration versus time profiles are presented in Figure 1.

Figure 1. Arithmetic Mean (+SD) Plasma Concentration versus Time Profiles of Macitentan (upper) and Aprocitentan (lower) after Administration of OPSUMIT (Treatment A) and After Administration of the Pediatric Macitentan CSF Formulation (Treatment B)



Source: Figure 11-1, Study AC-055-121 CSR

PK parameters of macitentan and aprocitentan (ACT-132577) are summarized in **Table 13** and **Table 14**, respectively.

Table 13. Comparison of the Main PK Parameters for Macitentan (Study AC-055-121)

PK Parameter (Macitentan)	N	Geometric Mean [a]		Comparison		
		Treatment A: Film-coated tablet approved for adults (1 × 10 mg macitentan)	Treatment B: Dispersible tablet for pediatric use (2 × 5 mg macitentan)	GMR (B/A) [b]	90% CI	p-value
C_{max} [ng/mL]	12	130.80	149.12	1.140	1.0420, 1.2475	0.025
AUC_{0-t} [ng × h/mL]	12	4,829.45	4,705.52	0.974	0.9009, 1.0537	0.561
$AUC_{0-\infty}$ [ng × h/mL]	12	4,873.86	4,747.47	0.974	0.9018, 1.0522	0.551
$t_{1/2}$ [h]	12	16.711	16.357	0.979	0.9186, 1.0431	0.556
t_{max} [h]	12	8.00	8.00	0.000 [b]	-0.5000, 0.5000	1.000

[a] Median for t_{max}.
[b] Difference in medians (B-A) for t_{max}.

Source: Table 7, Module 2.7.1

Table 14. Comparison of the Main PK Parameters for Metabolite Aprocitentan

(Study AC-055-121)

PK Parameter (Aprocitentan)	N	Geometric Means [a]		Comparison		
		Treatment A: Film-coated tablet approved for adults (1 × 10 mg macitentan)	Treatment B: Dispersible tablet for pediatric use (2 × 5 mg macitentan)	GMR (B/A) [b]	90% CI	p-value
C_{max} [ng/mL]	12	127.38	132.85	1.043	0.9618, 1.1309	0.369
AUC_{0-t} [ng × h/mL]	12	14,438.15	14,964.74	1.037	0.9861, 1.0895	0.222
$AUC_{0-\infty}$ [ng × h/mL]	12	15,420.35	15,921.37	1.033	0.9760, 1.0923	0.328
$t_{1/2}$ [h]	12	43.814	43.166	0.985	0.9180, 1.0573	0.710
t_{max} [h]	12	48.39	48.00	-0.250 [b]	-12.1000, 1.7700	0.401

[a] Median for t_{max}.
[b] Difference in medians (B-A) for t_{max}.

Source: Table 8, Module 2.7.1

Conclusion: The 90% confidence intervals (CI) of Cmax and AUCs fell within the established bioequivalence (BE) limits of 80.00–125.00% and therefore, it was concluded that the BA of the two formulations were comparable.

5.2.3. Study PAH1008: Relative BA Study (Final Phase 3/To-be-marketed (TBM) Formulation [FMI] vs. Initial Phase 3 Formulation [CSF])

For the Phase 3 trial (AC-055-312 [TOMORROW]), the pediatric dispersible tablet formulation of macitentan was initially provided as CSF at strengths of 0.5 mg, 2.5 mg, and 5 mg, and then, replaced by the final Phase 3/proposed TBM commercial formulation (FMI). This study was conducted to assess the relative BA of 10 mg macitentan given as CSF and FMI formulations.

This was a single-center, open-label, randomized, 2-treatment, single-dose, 2-period crossover study. A total of 16 healthy adult male and female participants were randomly assigned to 1 of 2 treatment sequences (A-B or B-A). Treatments A and B each consisted of a single 10 mg dose of macitentan using 2 different formulations:

- Treatment A (Test): 10 mg dose given as 4 dispersible 2.5 mg tablets formulated as FMI (G019).
- Treatment B (Reference): 10 mg dose given as 2 dispersible 5 mg tablets formulated as CSF (G013).

Both treatments were suspended in a tablespoon of water, approximately 10 to 15 mL taken from 240 mL, for 5 min. The participants were administered the suspended study intervention, followed by drinking the remaining water.

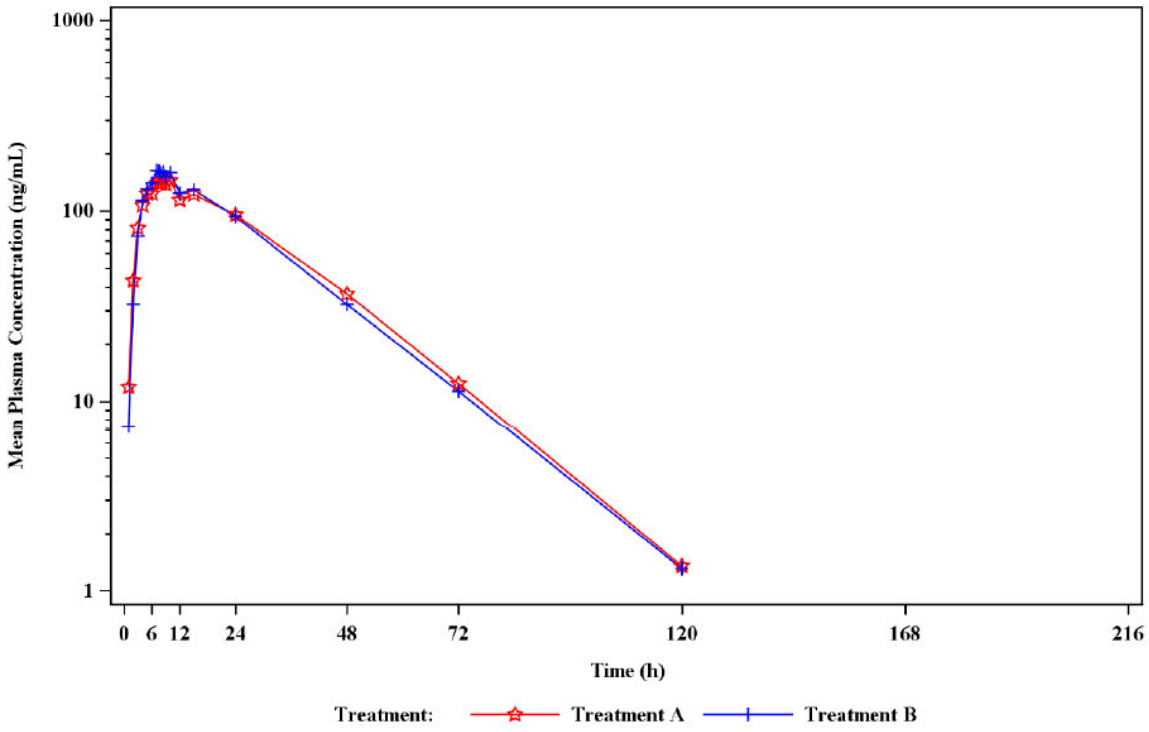
Treatments were administered under fasting conditions. Each observation period lasted 216 hours, with treatment periods separated by a washout period of at least 10 days (the day of study intervention intake in the previous treatment period was the first day of the washout period). Blood samples for analysis of macitentan and its active metabolite, aprocitentan (ACT-132577) were taken at prespecified time points (i.e., at pre-dose, 1, 2, 3, 4, 5, 6, 7, 7.5, 8, 8.5, 9, 10, 12, 15, 24, 48, 72, 120, 168, and 216 hours post-dose).

Two of 16 participants, randomized to treatment sequence A-B, withdrew study participation after completion of the first treatment period and therefore no PK data were available for the second treatment period (i.e., Treatment B) for these participants. For each treatment, descriptive statistics were calculated for plasma concentrations of macitentan and its metabolite, aprocitentan at each applicable timepoint specified, and for the derived plasma PK parameters. The statistical analysis (linear mixed-effects analysis of covariance [ANOVA] model, with treatment, treatment sequence, and period as fixed effects, and participant as random effect) used to compare key PK parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) was therefore based on 14 participants as only paired observations for test and reference were included in the statistical analysis.

There were no major protocol deviations, concomitant medication issues, or violations of the inclusion and exclusion criteria that led to exclusion of subjects from any analysis set.

Mean plasma concentration-time profiles of macitentan and aprocitentan in semi-log scale are presented in Figure 2 and Figure 3, respectively.

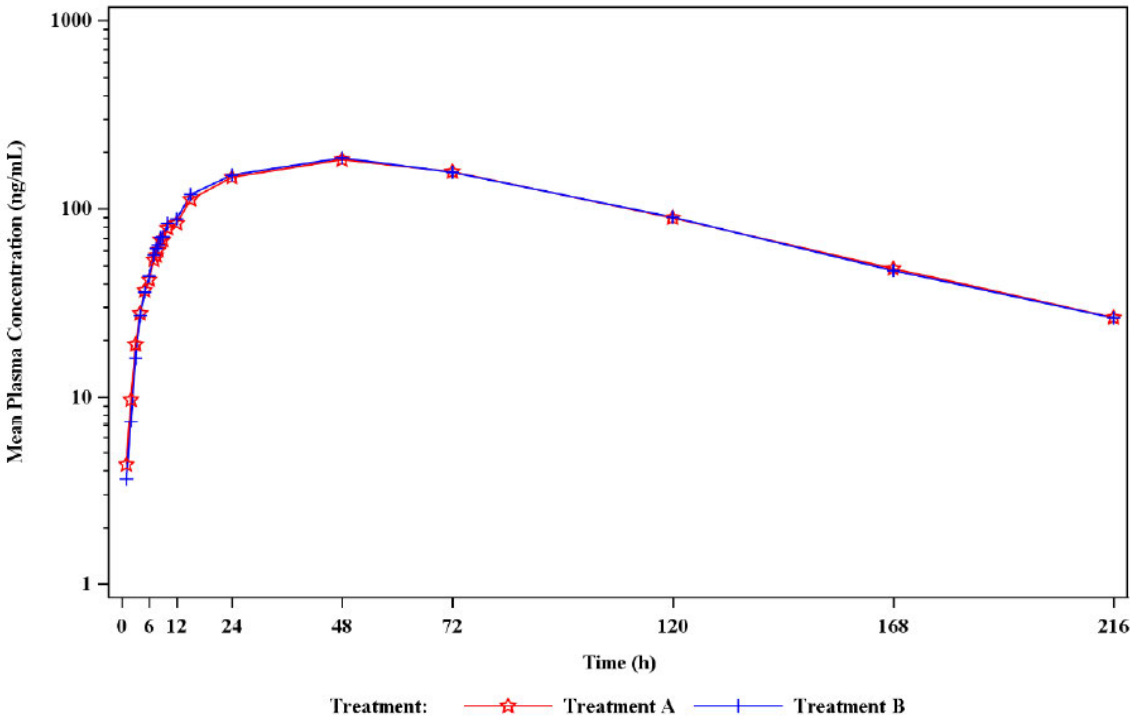
Figure 2. Mean Plasma Concentrations of Macitentan versus Time; PK Population (Study PAH1008)



Semi-log scale; From 0 to 216 h
Treatment A: A single oral dose of 10 mg macitentan formulated as Final Market Image (FMI) (dispersible tablets, 2.5 mg per tablet (G019)) in fasted conditions
Treatment B: A single oral dose of 10 mg macitentan as the Clinical Service Formulation (CSF) (dispersible tablets, 5 mg per tablet (G013)) in fasted conditions

Source: Figure 2, Study PAH1008 CSR

Figure 3. Mean Plasma Concentrations of Aprocitentan versus Time; PK Population (Study PAH1008)



Semi-log scale; From 0 to 216 h
Treatment A: A single oral dose of 10 mg macitentan formulated as Final Market Image (FMI) (dispersible tablets, 2.5 mg per tablet (G019)) in fasted conditions
Treatment B: A single oral dose of 10 mg macitentan as the Clinical Service Formulation (CSF) (dispersible tablets, 5 mg per tablet (G013)) in fasted conditions

Source: Figure 3, Study PAH1008 CSR

PK parameters of macitentan and aprocitentan are summarized in **Table 15** and **Table 16**, respectively.

Table 15. Comparison of Primary PK Parameters for Macitentan Based on ANCOVA Analysis (Study PAH1008)

PK Parameter (Macitentan)	N	Geometric LS Means		Test vs Reference		Variability		Post-hoc Power (%)
		Test (A): FMI	Reference (B):CSF	GMR (%)	90% CI (%)	Intra-participant CV (%)	Inter-participant CV (%)	
C_{max} [ng/mL]	14	155	176	87.76	83.58, 92.16	7.2	19.3	94.3
AUC_{0-t} [ng × h/mL]	14	4,997	4,936	101.24	97.59, 105.02	5.4	20.7	100.0
$AUC_{0-\infty}$ [ng × h/mL]	14	5,086	5,038	100.95	97.59, 104.42	5.0	20.0	100.0

Test=Treatment A: A single oral dose of 10 mg macitentan formulated as FMI (dispersible tablets, 2.5 mg per tablet [G019]) in fasting conditions.
Reference=Treatment B: A single oral dose of 10 mg macitentan formulated as CSF (dispersible tablets, 5 mg per tablet [G013]) in fasting conditions.

Source: Table 5, Module 2.7.1

Table 16. Comparison of Primary PK Parameters for Aprocitentan Based on ANCOVA Analysis (Study PAH1008)

PK Parameter (Aprocitentan)	N	Geometric LS Means		Test vs Reference		Variability		Post-hoc Power (%)
		Test (A): FMI	Reference (B): CSF	GMR (%)	90% CI (%)	Intra-participant CV (%)	Inter-participant CV (%)	
C_{max} [ng/mL]	14	179	185	96.74	92.55, 101.12	6.5	18.0	100.0
AUC_{0-t} [ng × h/mL]	14	20,841	21,048	99.02	95.65, 102.50	5.1	17.2	100.0
$AUC_{0-\infty}$ [ng × h/mL]	14	23,049	23,191	99.39	95.55, 103.39	5.8	19.7	100.0

Test=Treatment A: A single oral dose of 10 mg macitentan formulated as FMI (dispersible tablets, 2.5 mg per tablet [G019]) in fasting conditions.
Reference=Treatment B: A single oral dose of 10 mg macitentan formulated as CSF (dispersible tablets, 5 mg per tablet [G013]) in fasted conditions.

Source: Table 6, Module 2.7.1

Conclusion: The 90% CIs of C_{max} and AUCs all fell within the established BE limits of 80.00–125.00% and therefore, it was concluded that the BA of the two formulations were comparable.

5.2.4. Study PAH1010: Relative BA Study (Final Phase 3/TBM Formulation [FMI] vs. OPSUMIT)

This study was conducted to assess the relative BA of 10 mg macitentan given as FMI formulation and the approved film-coated OPSUMIT tablet.

This was a single-center, open-label, randomized, 2-treatment, single-dose, 2-period crossover study. A total of 28 healthy adult male and female participants were randomly assigned to 1 of 2 possible treatment sequences (A-B or B-A). Treatments A and B each consisted of a single 10 mg dose of macitentan using 2 different formulations:

- Treatment A (Test): 10 mg dose given as 4 dispersible 2.5 mg tablets (FMI [G019] formulation)
- Treatment B (Reference): 10 mg dose given as one film-coated OPSUMIT tablet (G001)

It is unclear if the pediatric formulation (i.e., FMI) was suspended in water like in the other 2 relative BA studies above. The OPSUMIT tablet was taken with approximately 240 mL of noncarbonated water.

Treatments were administered under fasting conditions. Each observation period lasted 216 hours, with treatment periods separated by a washout period of at least 10 days (the day of study intervention intake in the previous treatment period was the first day of the washout period). Blood samples for analysis of macitentan and its active metabolite, aprocitentan were taken at prespecified time points (i.e., at pre-dose, 1, 2, 3, 4, 5, 6, 7, 7.5, 8, 8.5, 9, 10, 12, 15, 24, 48, 72, 120, 168, and 216 hours post-dose).

All 28 participants received at least 1 dose of any study intervention. One participant (Subject (b) (6)) was excluded from the PK Data Analysis Set (i.e., included all participants who received at least 1 dose of study intervention and had at least 1 plasma concentration data value) and the PK Data Statistical Analysis Set (i.e., included all participants who received all planned doses of the study interventions) due to a major protocol deviation (i.e., prohibited medication). Therefore, 27

participants were included in the main PK analyses. For Subject (b) (6) with the missing 3 last samples (i.e., 120, 168, and 216 hours post-dose) in Treatment A, the following macitentan and aprocitentan PK parameters were considered unreliable due to missing concentrations: C_{last}, AUC_{last}, AUC_{∞} (where estimable), treatment ratios for AUCs (where estimable), CL/F, and Vd_z/F (both for macitentan only). Those parameters were excluded from the descriptive statistics. In addition, macitentan AUC_{last} and AUC_{∞} for this participant were excluded from the inferential statistical analyses as only paired observations were included. It should be noted that all participants except 1 showed quantifiable pre-dose concentrations of aprocitentan in Period 2. For 3 participants (Subjects (b) (6)) following administration of Treatment B and 1 participant (Subject (b) (6)) following administration of Treatment A, the quantifiable pre-dose concentration of aprocitentan was greater than 5% of the corresponding C_{max}. For those 4 profiles, all PK concentrations and PK parameters of aprocitentan were excluded from the descriptive statistics.

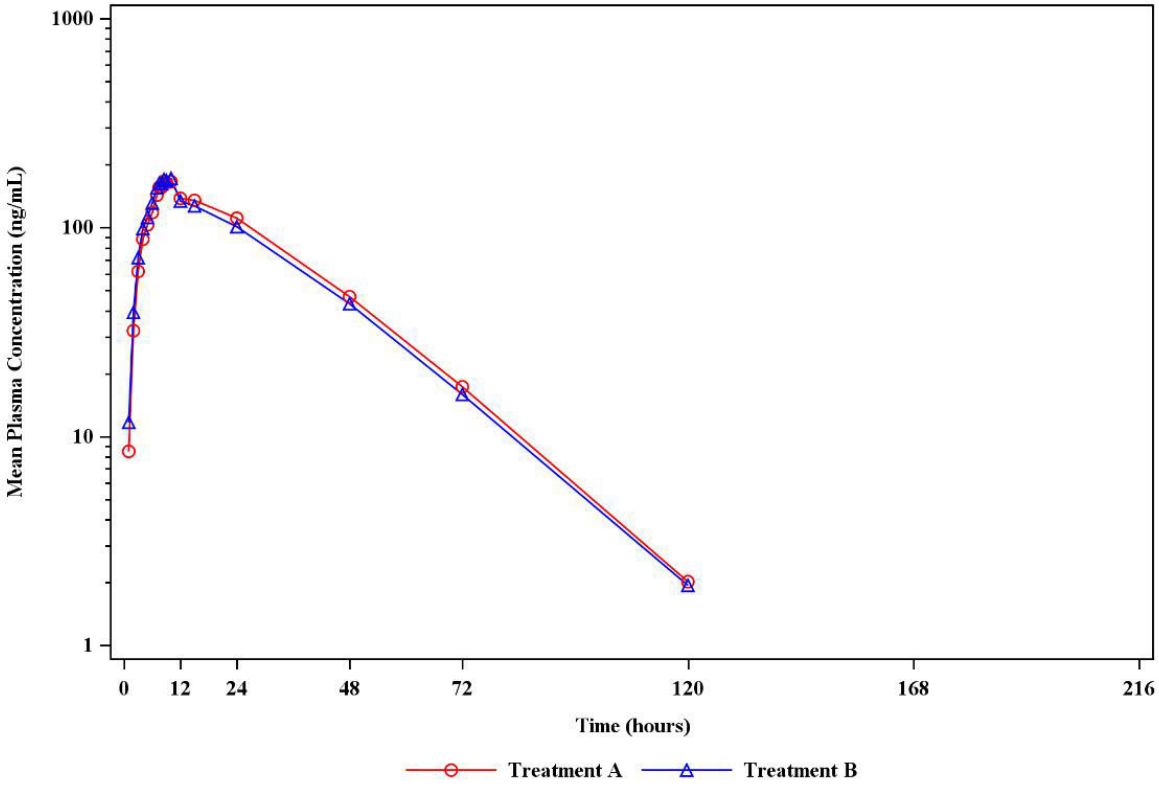
For each study intervention, descriptive statistics were calculated for plasma concentrations of macitentan and its metabolite aprocitentan, as applicable, at each applicable time point specified, and for the derived plasma PK parameters. The least-square (LS) means of the log-transformed primary PK parameters of macitentan for each treatment were estimated with a linear mixed effects model, controlling for treatment, sequence, and period as fixed effects, and participant as a random effect.

There were no other major protocol deviations, concomitant medication issues, or violations of the inclusion and exclusion criteria that led to exclusion of subjects from any analysis set.

Mean plasma concentration-time profiles of macitentan and aprocitentan in semi-log scale are presented in **Figure 4** and **Figure 5**, respectively.

Figure 4. Mean Plasma Concentrations of Macitentan versus Time; PK Data Analysis Set

(Study PAH1010)

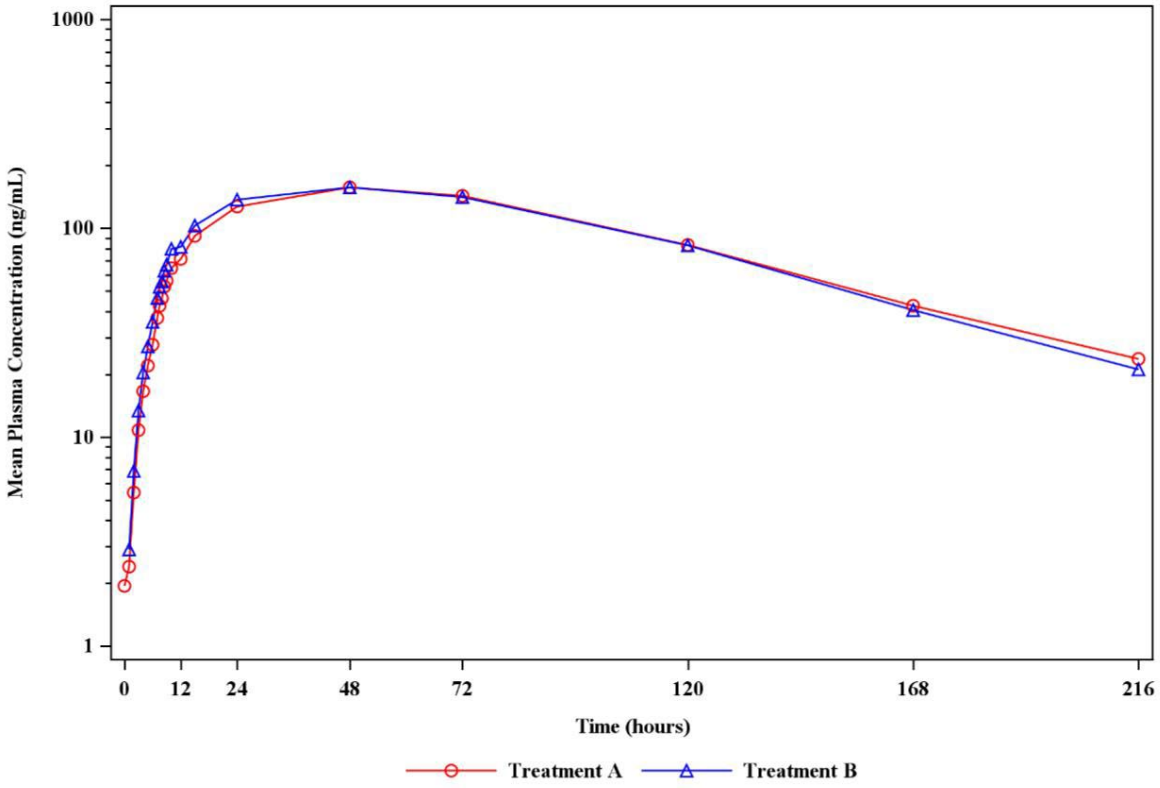


Semi-log scale; From 0 to 216 hours
Treatment A: Single oral dose of 10 mg (4 x 2.5 mg) of macitentan formulated as FMI in fasted conditions (test)
Treatment B: Single oral film-coated 10 mg Opsumit® tablet in fasted conditions (reference)

Source: Figure 2, Study PAH1010 CSR

Figure 5. Mean Plasma Concentrations of Aprocitentan versus Time; PK Data Analysis Set

(Study PAH1010)



Semi-log scale; From 0 to 216 hours
Treatment A: Single oral dose of 10 mg (4 x 2.5 mg) of macitentan formulated as FMI in fasted conditions (test)
Treatment B: Single oral film-coated 10 mg Opsumit® tablet in fasted conditions (reference)

Source: Figure 3, Study PAH1010 CSR

PK parameters of macitentan and aprocitentan are summarized in **Table 17** and **Table 18**, respectively.

Table 17. Summary of Statistical Analysis of Primary PK Parameters for Macitentan – PK Data Statistical Analysis Set (Study PAH1010)

	Geometric Mean			Treatment A vs Treatment B		Source of Variability	
PK Parameter	n	Treatment A (test)	Treatment B (reference)	GMR (%)	90% CI (%)	Intraparticipant CV (%)	Interparticipant CV (%)
C_{max} (ng/mL)	27	174	184	94.56	87.94-101.69	15.7	12.3
AUC_{last} (ng.h/mL)	26	5,704	5,508	103.54	99.49-107.77	8.4	20.9
AUC_{∞} (ng.h/mL)	26	5,818	5,594	104.01	100.07-108.11	8.1	20.5

n: Number of paired observations; GMR: Geometric mean ratio; CI: Confidence interval; CV: Coefficient of variation
Treatment A: Single oral dose of 10 mg (4 x 2.5 mg) of macitentan formulated as FMI in fasted conditions (test)
Treatment B: Single oral film-coated 10 mg Opsumit® tablet in fasted conditions (reference)

Source: Table 5, Study PAH1010 CSR

Table 18. Summary of Primary PK Parameters for Aprocitentan – PK Data Analysis Set

(Study PAH1010)

Pharmacokinetics of Aprocitentan mean (SD), t_{max}: median (range)	Treatment A (test)	Treatment B (reference)
n	26[a]	24
C_{max} (ng/mL)	158 (35.9)	165 (42.7)
t_{max} (h)	48.00 (23.91 - 72.20)	48.00 (23.97 - 72.18)
AUC_{72h} (ng.h/mL)	8,634 (1,987)	8,944 (2,096)
C_{last} (ng/mL)	23.7 (10.3)	21.1 (7.62)
AUC_{last} (ng.h/mL)	18,520 (4,025)	18,777 (4,312)
AUC_{∞} (ng.h/mL)	20,047 (4,529)	20,324 (4,804)
$t_{1/2}$ (h)	53.8 (9.9)	49.6 (5.7)

[a]: n=25 for C_{last}, AUC_{last}, and $t_{1/2}$; n=24 for AUC_{∞}.
Treatment A: Single oral dose of 10 mg (4 x 2.5 mg) of macitentan formulated as FMI in fasted conditions (test)
Treatment B: Single oral film-coated 10 mg Opsumit® tablet in fasted conditions (reference)

Source: Table 6, Study PAH1010 CSR

The Applicant only submitted a summary of PK parameters without the statistical analysis as aprocitentan was not the primary analyte of interest.

Conclusion: The 90% CIs of C_{max} and AUCs all fell within the established BE limits of 80.00-125.00% and therefore, it was concluded that the BA of the two formulations were comparable.

It should be noted that Studies PAH1008 and PAH1010 evaluated the higher 2.5 mg strength of the FMI. Evaluation of the lower 1.0 mg strength was considered not necessary, and the Applicant requested a biowaiver based on the following:

- The PK of macitentan was found to be dose-proportional in the dose range of 1-30 mg upon multiple dosing.
- The 2.5 mg and 1 mg FMIs are dose-proportional formulations.
- Both strengths are IR tablets with systemic action produced according to the same (b) (4) manufacturing process (b) (4)
- Both strengths were similar in vitro dissolution in 3 different pH media, as well as based on the proposed quality control (QC) method.

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

6.1.1. Macitentan Dosing Regimen

The 10 mg macitentan dose for the three relative BA studies was selected with the purpose to bridge the pediatric formulations to the approved adult macitentan dose (i.e., 10 mg). See Section 6.1.2 for the dose selection for the TOMORROW study.

6.1.2. Selection of Dosing Regimen for TOMORROW

The macitentan dosage regimen used in the TOMORROW study, with dosing according to age and body weight categories, was selected using model-based simulations to achieve systemic exposure observed in adults with PAH treated with macitentan 10 mg QD in a majority of the pediatric population. See Section 13.2 for details on population PK analysis and PK simulations.

6.2. Clinical Study Intended to Demonstrate Efficacy

6.2.1. Study AC-055-312 (TOMORROW)

6.2.1.1. Design

TOMORROW (Amendment 8, Version 9) was a prospective, multicenter, open-label, randomized, controlled, parallel group, Phase 3 study with an open-label single-arm extension period to evaluate PK, safety and efficacy of macitentan in children with PAH. As previously noted, TOMORROW was initially designed as a multicenter, open-label, randomized, parallel-group, group-sequential, event-driven study to assess the efficacy, safety, and PK of macitentan versus SoC in children with PAH. The primary efficacy endpoint was time to the first disease progression event. However, the Applicant changed the study to a PK study because of difficulty enrolling participants into the study.

157 subjects were enrolled based on feasibility. Subjects ≥ 2 years at Visit 2 were to be randomized in a 1:1 ratio to either receive macitentan or continue SoC. Randomization was stratified by ongoing/planned ERA treatment at randomization (yes vs no) and by WHO FC at randomization (FC I/II vs FC III). According to the protocol, the proportion of subjects with ERA treatment, as a component of the planned SoC, was to be limited to a maximum of 40% of the overall number of subjects. Of note, during discussions of the design of the development program, the Division voiced concern about permitting the use of an ERA in the SoC arm and specifically voiced concern that a failed trial that compares macitentan, an ERA, with standard of care that includes another ERA would be uninterpretable. The Applicant contended that prohibiting such use would making it challenging to enroll patients into the trial, given the widespread use of ERAs in the pediatric population, and thus implemented a cap on enrollment.

The cohort of children <2 years was not randomized but entered directly into the macitentan arm. The ERA cap did not apply to this cohort.

As shown in **Figure 6**, the study consisted of the following periods:

Screening Period: Started from signed informed consent and ended with randomization or confirmation of screening failure (up to 6 weeks after signed informed consent). Cohort of children <2 years: The screening period ended with confirmation of eligibility (i.e., age at Visit 2 was less than 2 years) and assignment of macitentan kit at Visit 2, or with screening failure.

Core Period: Commenced with Visit 2 and continued until the End of Core Period (EOCP) visit.

- Pre-Event Study Phase (Pre-Event SP): Started from Visit 2 until disease progression event confirmed by the CEC or until EOCP visit, whichever came first. During this period, any

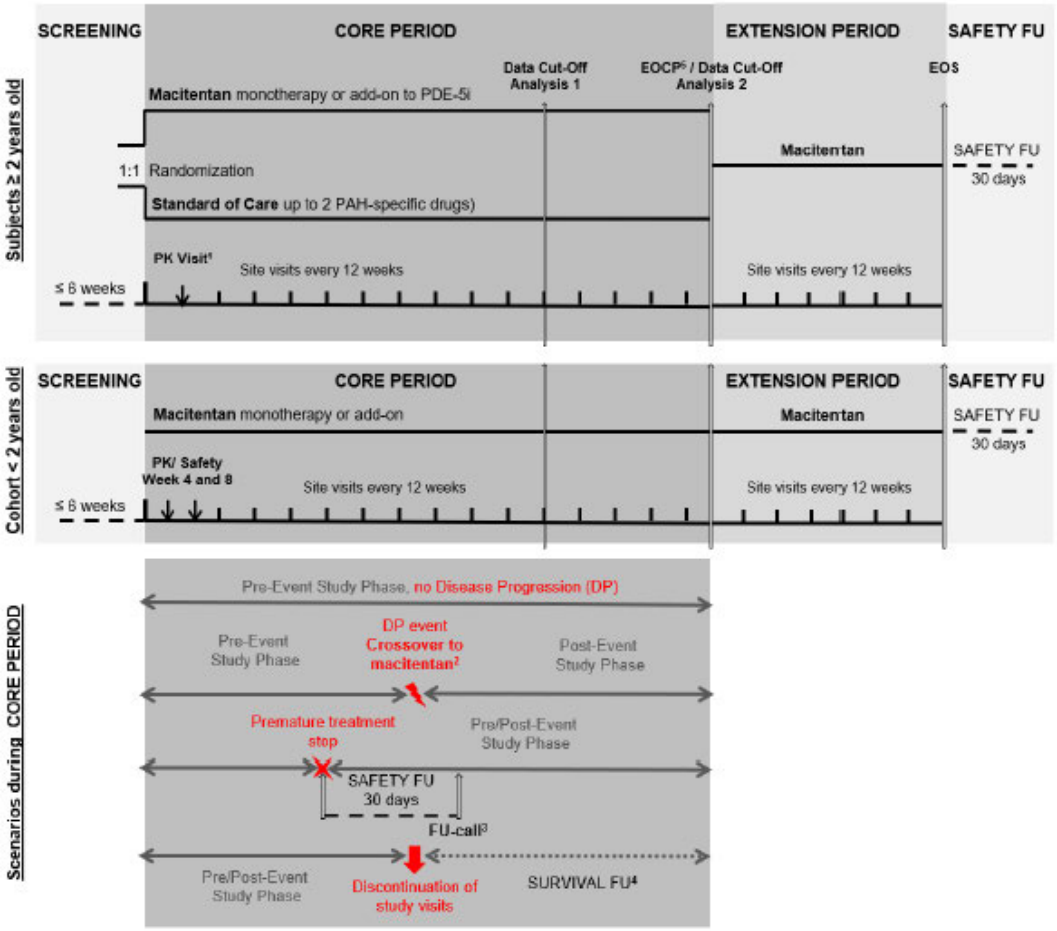
PAH-specific treatment (other than macitentan and IV/SC prostanoids) as either mono- or double combination therapy prescribed as SoC before randomization could be administered in the SOC arm. In the macitentan arm, PDE-5 inhibitor treatment ongoing at randomization could continue.

- Post-Event Study Phase (Post-Event SP): Began with CEC-confirmed disease progression event and continued until EOCP visit. During Post-Event SP PAH-specific background treatment may be escalated in both treatment arms as per local practice. Any additional treatment, including IV or SC prostanoids may be used in both treatment arms. Subjects in the macitentan arm could continue receiving macitentan. Subjects in the SoC arm were offered to cross-over to macitentan treatment, if this was in their best interests per their investigator's judgment.
- End of Macitentan: All subjects treated with macitentan who prematurely discontinued macitentan.
- Survival Follow-up: Applied to subjects who prematurely discontinued regular study visits during Core Period. Survival data were collected at least yearly after the last regular study visit and until EOCP for Analysis 2. In these subjects, the last survival follow-up contact constituted their EOS.
- End of Core Period (EOCP) Visit: This visit occurred in first quarter of 2024 and before the cutoff date for Analysis 2 which was announced by the Applicant. For subjects who didn't enter the Single-Arm Extension Period, the EOCP visit constituted their End-of-Study visit. The subjects who received macitentan had an EOM visit within 1 week after the last dose of macitentan.

Single-arm Extension Period: This period started at EOCP visit and ended at EOS visit. Subjects who were in the 12-weekly regular visits at EOCP visit, and for whom the investigator judged that macitentan treatment could be beneficial and who fulfilled the safety criteria to initiate or continue macitentan treatment were eligible to enter the open-label single-arm extension period.

Safety Follow-up Period: Applied to subjects who prematurely discontinued macitentan or SoC treatment during Core Period or during the single-arm extension period. In addition, it applied to subjects at EOS who did not enter the extension period or who did not go into a LTE study. It began immediately after premature end of treatment or after EOCP/EOS and ended at least 30 days later with a safety follow-up telephone call.

Figure 6. TOMORROW Study Design



EOS = end of study; FU = follow-up; IV = intravenous; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase Type 5 inhibitor; PK = pharmacokinetics; SC = subcutaneous.

Source: Figure 1, AC-055-312 protocol.

6.2.1.2. Eligibility Criteria

Subjects were included if they met the following criteria.

1. Signed informed consent by the parent(s) or legally designated representative AND assent from developmentally capable children prior to initiation of any study-mandated procedure.
2. Males or females between ≥ 1 month and <18 years of age.
3. Subjects with body weight ≥3.5 kg at randomization.
4. PAH diagnosis confirmed by historical RHC (mean PAP ≥ 25 mm Hg, and PAWP ≤ 15 mm Hg, and PVRi > 3 WU x m^2), where in the absence of pulmonary vein obstruction and/or significant lung disease PAWP can be replaced by left atrial pressure or left ventricular end diastolic pressure (in absence of mitral stenosis) assessed by heart

catheterization (Criterion modified per Amendment 6).[6]

5. PAH belonging to the Nice 2013 Updated Classification Group 1 (including subjects with Down Syndrome) and of the following etiologies:
   - iPAH
   - hPAH
   - PAH associated with CHD:
     - PAH with co-incidental CHD
     - Post-operative PAH (persisting/recurring/developing ≥ 6 months after repair of CHD)
   - Drug or toxin-induced PAH
   - PAH associated with human immunodeficiency virus
   - PAH associated with connective tissue disease
6. WHO FC I to III.
7. PAH-specific treatment-naïve subjects or subjects on PAH-specific treatment (mono-therapy or combination of two therapies). Treatments other than PDE-5 inhibitors, such as prostanoids, could not be continued in the macitentan arm, and therefore had to be stopped if the patient was randomized into the macitentan arm.
8. Females of childbearing potential must have a negative pregnancy test at Screening and at Baseline, and must agree to undertake monthly pregnancy tests, and to use a reliable method of contraception (if sexually active) up to EOS.

Key exclusion criteria included the following.

1. Subjects with PAH due to portal hypertension, schistosomiasis, pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis, and persistent pulmonary hypertension of the newborn.
2. Subjects with PAH associated with open shunts, as specified below:
   a. Eisenmenger syndrome
   b. Moderate to large left-to-right shunts.
3. Subjects with the following congenital cardiac abnormalities:
   a. Cyanotic congenital cardiac lesions such as transposition of the great arteries, truncus arteriosus, pulmonary atresia with ventricular septal defect, unless operatively repaired and with no residual shunt
   b. Univentricular heart and/or subjects with Fontan-palliation.
4. Subjects with pulmonary hypertension due to lung disease (e.g., bronchopulmonary

[6] Prior to Amendment 6, the inclusion criteria were PAH diagnosis ≤ 5 years before randomization, confirmed by historical RHC (mPAP ≥ 25 mmHg, and PAWP ≤ 15 mmHg, and PVRi > 3 WU × m2), where in the absence of pulmonary vein obstruction and/or significant lung disease PAWP can be replaced by LAP or LVEDP (in absence of mitral stenosis) assessed by heart catheterization.

dysplasia).

5. Subjects with known diagnosis of bronchopulmonary dysplasia.
6. Subjects receiving a combination of > 2 PAH-specific treatments at randomization.
7. Treatment with IV or SC prostanoids within 4 weeks before randomization, unless given for vasoreactivity testing.

6.2.1.3. Statistical Analysis Plan, AC-055-312 (TOMORROW) Study

The final analysis for the TOMORROW study covered only the data collected during the core period (randomization period) and was based on the Statistical Analysis Plan Version 5.0 dated March 13, 2023. The statistical analyses for the single-arm extension and safety follow-up periods were not included in the statistical analysis plan.

Given that the study's secondary objectives were to investigate the efficacy and safety in subjects who were greater or equal to 2 years old, the statistical review focused on the efficacy findings in this population.

Efficacy Analysis Sets

1. Full Analysis Set 1 (FAS1) – This set includes all participants randomized to a study treatment arm (i.e. all randomized participants ≥ 2 years old at randomization). This set is the study intent-to-treat set and used for primary efficacy analyses for the efficacy endpoints. The participants are analyzed based on their assigned treatment arm at randomization. All available data during EOCP are included in the analysis.
2. Full Analysis Set 2 (FAS 2) - This set includes all participants who are less than 2 years old and enrolled in the core period. This set is for exploratory purposes.
3. Full Analysis Set 3 (FAS 3) – This set includes all participants and data in FAS1 and FAS2.

Efficacy Endpoints

The revised primary endpoint of the study is a PK endpoint. All efficacy endpoints are therefore secondary by design.

The first secondary endpoint is the time to first CEC-confirmed disease progression events[7] occurring between randomization and EOCP. Disease progression is defined as the first emergence of the following events:

1) Death (all causes)
2) Atrial septostomy or Potts' anastomosis, or on lung transplant list
3) Hospitalization due to worsening PAH, excluding hospitalizations that are elective, routine, or clearly attributable to appearance/worsening of comorbidities (e.g.,

[7] Different terminology have been used to describe the endpoint in PAH development programs. Current Division practice is to refer to this endpoint as "clinical worsening events" in product labeling.

pneumonia)

4) Clinical worsening of PAH (from baseline) defined as:

a) one of these:

i. Worsening in WHO functional class

ii. New occurrence or worsening of syncope or at least 2 PAH symptoms (i.e., shortness of breath/dyspnea, chest pain, cyanosis, dizziness/near syncope, or fatigue)

iii. New occurrence or worsening of signs of right heart failure not responding to oral diuretics

b) and need for or initiation of new PAH-specific therapy (e.g., endothelin receptor antagonists, PDE5i, prostanoids, soluble guanylate cyclase stimulators), intravenous diuretics, or continuous oxygen use.

Other secondary efficacy endpoints include:

1. Time to first CEC-confirmed hospitalization for PAH occurring between randomization and EOCP.
2. Time to CEC-confirmed death due to PAH occurring between randomization and EOCP
3. Time to death (all causes) occurring between randomization and study closure
4. WHO FC status (I or II vs III or IV) at Weeks 12 and 24
5. Percent of Baseline plasma NT-proBNP at Weeks 12 and 24
6. Change from Baseline to Week 48 in mean daily time spent in moderate to vigorous physical activity (MVPA) as measured by accelerometry
7. Change from Baseline to Week 24 in BSA-normalized TAPSE
8. Change from Baseline to Week 24 in LVEI measured by echocardiography (centrally assessed)
9. Change from Baseline to Week 24 in QoL as measured by the PedsQL™ 4.0 Generic Core Scales Short Form (SF15)

Given the purpose of this review and findings in the trial, the scope of the statistical review was limited to secondary clinical endpoints #1 to #5, as agreed upon with the clinical team. The Applicants results are shown for endpoints #6 to #9 in Section 15.

Multiplicity Adjustment

The Applicant did not prespecify any multiplicity adjustments in the study protocol or in the Statistical Analysis Plan.

Sample Size

The Applicant initially planned to enroll approximately 200 to 300 subjects to provide 187 primary endpoint events. This number of primary endpoint events was expected to achieve overall 80% statistical power to detect the hazard ratio (HR) of 0.65 under an overall two-sided type I error of alpha of 0.05. However, because of feasibility considerations, the Applicant revised the primary endpoint to a PK endpoint and terminated the study.

Secondary Endpoint Analyses

All analyses were based on FAS1.

Time-to-Event Efficacy Endpoint: Disease Progression Events[8]

All disease progression events occurring from randomization until the EOCP are considered, irrespective of subjects' compliance to assigned therapies.

Subjects who have not experienced any CEC-confirmed disease progression before EOCP will have their time to first disease progression right-censored at the time of EOCP or cutoff date for the respective analysis, whichever occurs first. For subjects who have prematurely discontinued regular study visits, the last survival follow-up contact will be used as the EOCP visit. Time to first CEC-confirmed disease progression will be calculated in days and calculated as the onset date of the first CEC-confirmed disease progression minus date of randomization. In case of concomitant events happening on the same day, the first one in hierarchical order will be summarized, where the hierarchical order is set in the same manner of the list when defining primary efficacy endpoint.

The survival functions of the two treatment arms will be compared using a two-sided stratified log-rank test adjusted for stratification factors at randomization. The treatment effect, in terms of hazard ratio, is estimated based on a proportional hazards Cox model adjusting for the stratification factors at randomization. The associated p-value and 95% confidence interval will also be calculated.

No additional imputation was done for the subjects with no CEC-confirmed event at the time of EOCP.

No intercurrent events were defined.

A stratified Kaplan Meier (KM) plot will be made. The number of subjects at risk, and the number of subjects with events will be computed at each timepoint and for each treatment group.

Time-to-Event Other Secondary Efficacy Endpoints (Endpoints 1–3)

All corresponding time to first CEC-confirmed event occurring from randomization until the EOCP period are considered, irrespective of subjects' compliance to assigned therapies.

For the endpoint of time to first CEC-confirmed hospitalization for PAH, the participants who died without any CEC-confirmed hospitalization for PAH are also included in the analysis as an event instead being of censored.

Subjects who have not experienced any event before the EOCP period will have their time to event right-censored at the time of EOCP visit or cutoff date for the respective analysis, whichever occurs first. For subjects who have prematurely discontinued regular study visits, the last survival follow-up contact will be used as the EOCP visit. Time to first CEC-confirmed disease progression will be calculated in days and calculated as the onset date of the event minus date of randomization.

The survival functions of the two treatment arms will be compared using a two-sided stratified log-rank test adjusted for stratification factors at randomization. The treatment effect, in terms of hazard ratio, is estimated based on a proportional hazards Cox model adjusting for the stratification factors at randomization. The associated p-value and 95% confidence interval will also be calculated.

[8] Different terminology have been used to describe the endpoint in PAH development programs. Current Division practice is to refer to this endpoint as "clinical worsening events" in product labeling.

No additional imputation was done for the subjects with no CEC-confirmed event at the time of EOCP. A stratified KM plot will be made. The number of subjects at risk, and the number of subjects with events will be computed at each timepoint and for each treatment group.

WHO FC status at Weeks 12 and 24

The proportion of subjects having WHO FC I or II will be summarized and compared between the two treatment groups only at Weeks 12 and 24 by means of a logistic regression adjusting for the two stratification factors: ongoing/planned ERA treatment (yes vs no) and WHO FC (FC I/II vs FC III) at randomization. The odds ratio (macitentan/SoC) will be displayed with 2-sided 95% confidence interval (CI).

In case of missing Week 12 values, in the logistic regression, subjects who are hospitalized due to PAH (CEC confirmed) or died prior to or at Week 12 (i.e. hospitalized before Week 12 visit date or died prior to last day of the related time-window), the value of WHO FC will be imputed as the worst case at Week 12 for analysis. The same imputation rule is applied to Week 24 but imputing the worst case at Week 24.

A sensitivity analysis imputing the missing values with the least favorable to macitentan will be conducted to examine the impact of the missing values beyond the imputation described above. That is, after the missing values being imputed for the subjects who are hospitalized due to PAH or died prior to Week 12 or Week 24, if the WHO FC at Week 12 (or 24) is still missing, the WHO FC will be imputed by class III and I for the macitentan arm and SoC arm, respectively.

Percent of Baseline plasma NT-proBNP at Weeks 12 and 24

The percent of baseline at Week 12 and at Week 24 in plasma NT-proBNP, defined as 100* (NTproBNP at timepoint / NT-proBNP at baseline), will be calculated.

The percent of baseline in NT-proBNP at each timepoint of assessment will be evaluated using a mixed model for repeated measure (MMRM) on the log-transformed percent of baseline in NT-proBNP between the timepoint and baseline on FAS1. The model will include randomized treatment, visit, treatment by visit interaction, and the 2 randomization stratification factors as fixed effects and log-transformed baseline NT-proBNP as fixed covariate, while participant will be included as a random effect. Each timepoint of assessment will be assessed with the comparison at Week 12 and Week 24 being the most relevant.

The treatment effect expressed as geometric means ratio and its associated 95% 2-sided CIs will then be estimated at each post-baseline timepoint of assessment by inversely transforming, using the exponential function, the difference in change from baseline between treatment groups and the associated 95% CIs, both estimated via the above model in log scale.

A plot of the mean absolute change in NT-proBNP profile over time will be provided on FAS1 considering observed NT-proBNP changes from baseline.

6.2.1.4. Study Results

Compliance with Good Clinical Practices

The protocol provided attestation that the studies were conducted in accordance with consensus

ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guideline. The conduct of the study was supervised by the DMC. Specified clinical events were reviewed on an ongoing basis by a CEC to determine if endpoint criteria were met.

Financial Disclosure

Financial disclosure information was provided (section 20). None of the investigators reported receiving compensation from the Applicant.

Patient Disposition

A total of 173 subjects were screened and 157 subjects were randomized across 51 sites in 18 countries. Most common reason for screen failure was 'Failure to meet randomization criteria' (*Applicant's Table LSIDS01*).

Subject disposition is shown in **Table 19**. One subject randomized to macitentan did not receive treatment because the subject withdrew consent and discontinued the study.

33% of subjects discontinued treatment — 41% of subject in the SoC arm compared to 23% of subjects in the Macitentan arm. The reasons for treatment discontinuation were physician's decision, parent/subject's decision and death.

19% of subjects withdrew from the study, and only 2% were lost to follow-up.

Table 19. Subject Disposition

TSIDS02: Subjects Disposition; FAS3 Analysis Set (Study AC-055-312)

	Randomized Macitentan	Randomized Standard of Care	Macitentan (< 2 Years Old)	Total
Analysis set: FAS3	73	75	9	157
Subjects enrolled < 2 years old	-	-	9 (100.0%)	9 (5.7%)
Subjects randomized ≥ 2 years old	73 (100.0%)	75 (100.0%)	-	148 (94.3%)
Subjects treated	72 (98.6%)	75 (100.0%)	9 (100.0%)	156 (99.4%)
Subjects ≥ 2 years old who prematurely discontinued randomized macitentan or SoC during the Core Period	17 (23.3%)	31 (41.3%)	-	48 (30.6%)
Subjects < 2 years old who prematurely discontinued macitentan during the Core Period	-	-	1 (11.1%)	1 (0.6%)
Crossover subjects	-	8 (10.7%)	-	8 (5.1%)
Subjects who prematurely withdrew from regular study visits during the Core Period	17 (23.3%)	21 (28.0%)	1 (11.1%)	39 (24.8%)
Subjects who prematurely withdrew from study	14 (19.2%)	15 (20.0%)	1 (11.1%)	30 (19.1%)
Subjects who are lost to follow-up in the Core Period	1 (1.4%)	2 (2.7%)	0	3 (1.9%)
Subjects who completed the Core Period	59 (80.8%)	60 (80.0%)	8 (88.9%)	127 (80.9%)
Subjects who enroll in single-arm extension study	48 (65.8%)	40 (53.3%)	8 (88.9%)	96 (61.1%)
Subjects who completed the study	9 (12.3%)	21 (28.0%)	0	30 (19.1%)

Key: SoC = Standard of care.

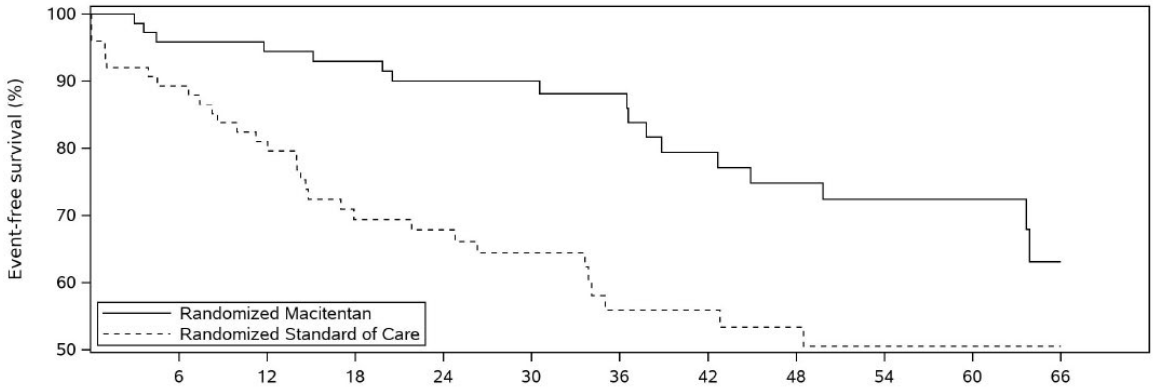
[tsids02.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_cco5/tsids02.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-28
Production Date: 07MAR2024, 08:35

Source: Table 4, AC-055-312 CSR End of Core Period

Treatment Exposure

Subjects in the SoC arm had a shorter extent of exposure as shown in **Figure 7**. Median duration of exposure was 169 weeks in the macitentan arm verses 143 weeks in the SoC arm. Median exposure was 27 weeks for subjects < 2 years.

Figure 7. Time Course of Treatment Exposure



Randomized Macitentan											
at risk|	69	66	64	58	49	42	35	31	29	20	11
event(s)|	3	4	5	7	7	8	12	14	15	15	17
censored|	0	2	3	7	16	22	25	27	28	37	44
Randomized Standard of Care											
at risk|	66	58	46	41	36	24	22	19	17	11	5
event(s)|	8	14	22	23	25	29	29	30	31	31	31
censored|	1	3	7	11	14	22	24	26	27	33	39

Key: EOCP = End of core period; SoC = Standard of care.
Note: Main treatment period: from randomization up to end of randomized macitentan or SoC + 30 days (or EOCP, whichever comes first), or for crossover subjects up to start of macitentan or end of SoC + 30 days, whichever comes first.
[gsidisc01ph.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_post_hoc/gsidisc01ph.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-28 ; Production Date: 15MAR2024, 05:36

Source: Figure 1, AC-055-312 CSR End of Core Period

Baseline Demographics and Disease Characteristics

There were some differences in randomized treatment groups with respect to baseline demographics (**Table 20**). The SoC arm had more younger subjects and fewer white subjects. Overall, subjects were predominantly female (60%), white (51%) and less than 12 years (65%).

Randomized treatment groups were generally balanced for key baseline disease characteristics (**Table 21**). Most subjects had idiopathic/heritable PAH (52%) and approximately 75% of subjects were WHO functional class II/III. Approximately 45% of subjects were on background treatment with PDE-5i + ERA or ERA monotherapy and approximately 51% of subjects were taking PDE-5i monotherapy.

Table 20. Baseline Demographics for Subjects ≥ 2 years, FAS1 Population

	Randomized Macitentan	Randomized Standard of Care	Total
Analysis set: FAS1	73	75	148
Age, years			
N	73	75	148
Mean (SD)	10.54 (4.430)	8.99 (4.320)	9.75 (4.429)
Median	10.30	8.00	9.60
Range	(2.1; 17.9)	(2.1; 17.8)	(2.1; 17.9)
IQ range	(7.50; 14.40)	(5.40; 12.90)	(6.20; 13.60)
≥ 2 - < 6 years	13 (17.8%)	22 (29.3%)	35 (23.6%)
≥ 6 - < 12 years	29 (39.7%)	32 (42.7%)	61 (41.2%)
≥ 12 - < 18 years	31 (42.5%)	21 (28.0%)	52 (35.1%)
Sex			
N	73	75	148
Female	50 (68.5%)	38 (50.7%)	88 (59.5%)
Male	23 (31.5%)	37 (49.3%)	60 (40.5%)
Race			
N	73	75	148
Asian	15 (20.5%)	22 (29.3%)	37 (25.0%)
Black or African American	1 (1.4%)	1 (1.3%)	2 (1.4%)
White	44 (60.3%)	32 (42.7%)	76 (51.4%)
Other	12 (16.4%)	18 (24.0%)	30 (20.3%)
Not Applicable	1 (1.4%)	2 (2.7%)	3 (2.0%)
Ethnicity			
N	73	75	148
Hispanic or Latino	24 (32.9%)	22 (29.3%)	46 (31.1%)
Not Hispanic or Latino	47 (64.4%)	51 (68.0%)	98 (66.2%)
Unknown	2 (2.7%)	2 (2.7%)	4 (2.7%)
Region			
N	73	75	148
North America	6 (8.2%)	6 (8.0%)	12 (8.1%)
Europe/Israel	28 (38.4%)	23 (30.7%)	51 (34.5%)
Asia/Australia	16 (21.9%)	24 (32.0%)	40 (27.0%)
Other	23 (31.5%)	22 (29.3%)	45 (30.4%)
Weight, kg			
N	73	75	148
Mean (SD)	36.36 (18.295)	30.58 (16.520)	33.43 (17.599)
Median	34.50	24.00	28.15
Range	(10.0; 75.5)	(10.0; 73.3)	(10.0; 75.5)
IQ range	(21.20; 51.00)	(17.00; 40.30)	(18.75; 47.30)
Height, cm			
N	73	75	148
Mean (SD)	134.96 (24.776)	128.75 (24.326)	131.81 (24.663)
Median	139.00	126.30	133.00
Range	(80.0; 176.0)	(79.0; 182.2)	(79.0; 182.2)
IQ range	(118.40; 155.20)	(111.00; 145.50)	(112.15; 152.00)
Down Syndrome			
N	73	75	148
Present	5 (6.8%)	5 (6.7%)	10 (6.8%)
Absent	68 (93.2%)	70 (93.3%)	138 (93.2%)

Key: IQ = Interquartile; SD = Standard deviation.
Note: N's for each parameter reflect non-missing values.
Percentage is calculated as the number of subjects in the category divided by N * 100.
[tsidem01.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_cco5/tsidem01.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-28
Production Date: 07MAR2024, 08:35

Source: Table 7, AC-055-312 CSR End of Core Period

Table 21. Key Baseline Disease Characteristics for Subjects ≥ 2 Years

	Randomized Macitentan	Randomized Standard of Care	Total
Analysis set: FAS1	73	75	148
Pulmonary arterial hypertension etiology			
N	73	75	148
Idiopathic PAH	35 (47.9%)	36 (48.0%)	71 (48.0%)
Heritable PAH	1 (1.4%)	5 (6.7%)	6 (4.1%)
PAH with co-incidental CHD	14 (19.2%)	12 (16.0%)	26 (17.6%)
PAH associated with CHD: post-operative	22 (30.1%)	20 (26.7%)	42 (28.4%)
PAH associated with connective tissue disease	1 (1.4%)	2 (2.7%)	3 (2.0%)
Time from PAH diagnosis to randomization, days			
N	73	75	148
Mean (SD)	698.4 (667.21)	667.2 (791.43)	682.6 (730.48)
Median	491.0	345.0	466.5
Range	(27; 3576)	(29; 4668)	(27; 4668)
IQ range	(131.0; 1157.0)	(100.0; 1031.0)	(105.5; 1076.0)
WHO functional class[2]			
N	73	75	148
I	19 (26.0%)	18 (24.0%)	37 (25.0%)
II	41 (56.2%)	42 (56.0%)	83 (56.1%)
III	13 (17.8%)	15 (20.0%)	28 (18.9%)
Panama functional class			
N	68	72	140
I	16 (23.5%)	19 (26.4%)	35 (25.0%)
II	42 (61.8%)	37 (51.4%)	79 (56.4%)
IIIa	10 (14.7%)	13 (18.1%)	23 (16.4%)
IIIb	0	3 (4.2%)	3 (2.1%)
Ongoing/planned ERA treatment at randomization as per IRT			
N	73	75	148
Yes	33 (45.2%)	34 (45.3%)	67 (45.3%)
No	40 (54.8%)	41 (54.7%)	81 (54.7%)
NT-pro BNP, pmol/L			
N	66	70	136
Mean (SD)	145.33 (414.72)	77.12 (141.14)	110.22 (306.86)
Median	18.23	21.18	20.59
Range	(2.36; 3052.90)	(1.06; 642.04)	(1.06; 3052.90)
IQ range	(7.55; 52.51)	(7.91; 41.42)	(7.85; 51.51)
Baseline BSA-normalized TAPSE[3], mm/m^2			
N	67	69	136
Mean (SD)	14.819 (5.2773)	17.525 (6.8239)	16.192 (6.2382)
Median	13.360	17.610	16.090
Range	(6.44; 29.37)	(5.11; 34.43)	(5.11; 34.43)
IQ range	(10.950; 18.700)	(11.780; 22.570)	(11.220; 20.645)
Baseline left ventricular eccentricity index (diastole)[3]			
N	66	64	130
Mean (SD)	1.462 (0.5036)	1.505 (0.5273)	1.483 (0.5139)
Median	1.380	1.365	1.370
Range	(0.90; 4.20)	(0.90; 4.40)	(0.90; 4.40)
IQ range	(1.100; 1.580)	(1.200; 1.670)	(1.200; 1.600)
Baseline left ventricular eccentricity index (systole)[3]			
N	66	64	130
Mean (SD)	1.815 (0.7144)	1.820 (0.8972)	1.817 (0.8064)
Median	1.535	1.550	1.535
Range	(0.90; 4.30)	(0.80; 5.45)	(0.80; 5.45)
IQ range	(1.300; 2.100)	(1.250; 2.065)	(1.300; 2.100)
Ongoing / Planned SoC at randomization (as per IRT)			
N	73	75	148
Non-PAH-specific therapies	3 (4.1%)	3 (4.0%)	6 (4.1%)

	Randomized Macitentan	Randomized Standard of Care	Total
PDE-5 inhibitor (PDE-5i) monotherapy	39 (53.4%)	36 (48.0%)	75 (50.7%)
ERA monotherapy	7 (9.6%)	5 (6.7%)	12 (8.1%)
PDE-5i + ERA	23 (31.5%)	29 (38.7%)	52 (35.1%)
PDE-5i + inhaled/oral prostanoids	1 (1.4%)	1 (1.3%)	2 (1.4%)
PDE-5i + sGC stimulator	0	1 (1.3%)	1 (0.7%)

Key: BSA = Body surface area; CHD = Congenital heart disease; ERA = Endothelin receptor antagonist; HIV = Human immunodeficiency virus; IQ = Interquartile; IRT = Interactive response technology; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PDE-5i = Phosphodiesterase type 5 inhibitor; SD = Standard deviation; sGC = Soluble guanylate cyclase stimulator; SoC = Standard of care; TAPSE = Tricuspid annular plane systolic excursion; WHO = World Health Organization.
[1] A subject may have more than one sign or symptom denoting PAH reported as present.
[2] Subjects with WHO functional class IV at baseline are not eligible as per inclusion criteria.
[3] As per central review of echocardiogram.
[tsidem04.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_cco5/tsidem04.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-28 ; Production Date: 07MAR2024, 08:35

Source: Table 9, AC-055-312 CSR End of Core Period

6.2.1.5. Efficacy Results

Secondary Efficacy Endpoint – Time to First Disease Progression Event

The primary analysis result of the endpoint – time to first disease progression event, is shown in **Table 22**. **Figure 8** shows the stratified KM plot for the FAS1 population with stratification factors WHO functional class (I/II vs III) and ongoing/planned ERA treatment (yes or no) at randomization.

The statistical reviewer's result is very close to the Applicant's result. There were 45 events, including 21 (29% of subjects) and 24 (32% of subjects) in the macitentan and SoC treatment arms, respectively. The stratified HR for the time to first disease progression event is 0.84 (95% CI: (0.47, 1.52)) and the unstratified HR is 0.8 (95% CI: (0.44, 1.44)). Although the point estimates of the HRs numerically favored the macitentan arm, the confidence intervals were wide and crossed 1 indicating that the results are inconclusive. Clinical worsening of PAH was the most common event in both arms, including 15 and 21 events in the macitentan and SoC arms, respectively. The findings across the components were not consistent (for some events the number was lower in the macitentan arm whereas for others, the number was lower in the SOC arm), although overall there were few events.

Table 22. Primary Analysis: Time to First Disease Progression Event in FAS1

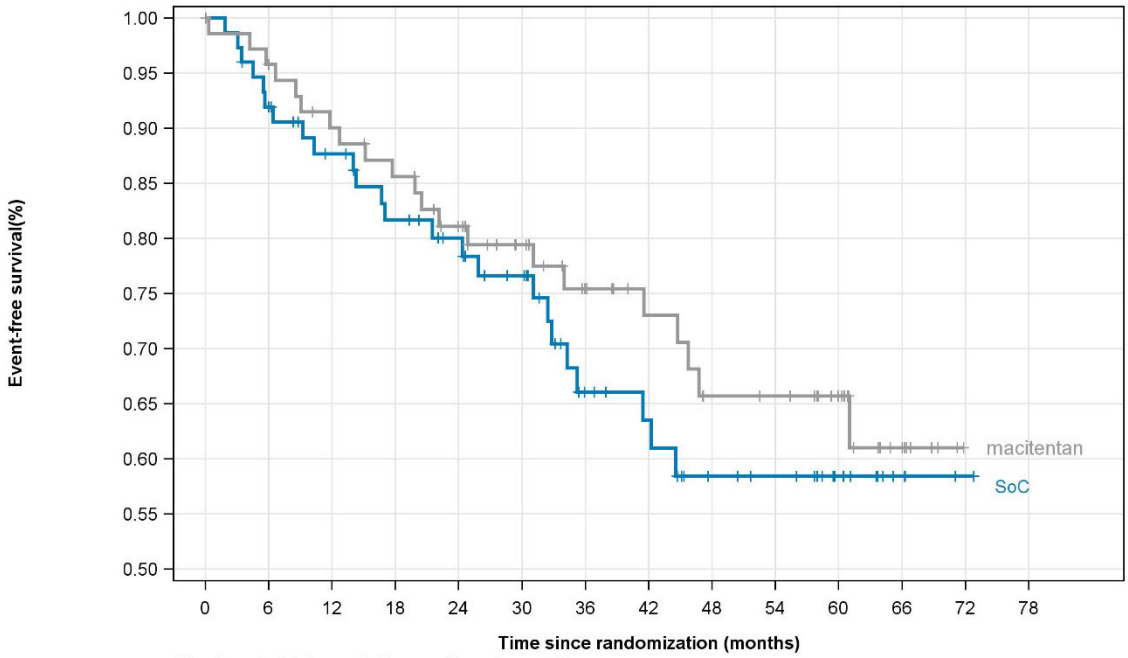
Time to First Disease Progression Event	Macitentan N=73	Standard of Care N=75
Events,[1] n (%)	21 (28.8)	24 (32.0)
Clinical worsening of PAH, n	15	21
Death (all causes), n	4	3
Hospitalization due to worsening PAH, n	2	0
Atrial septostomy or Potts anastomosis, or registration on lung transplant list, n	0	0
HR[2] (95% CI) (stratified)	0.84 (0.47,1.52)	-

Time to First Disease Progression Event	Macitentan N=73	Standard of Care N=75
p-value[3] (stratified)	0.57	-
HR[4] (95% CI) (unstratified)	0.80 (0.44, 1.44)	
p-value[5] (unstratified)	0.45	

Abbreviations: CI = confidence interval, HR = hazard ratio, FAS1 = Full Analysis Set 1, n/N = number of patients
[1]Incluce all participants ongoing in the study at the time of cutoff. For those who do not have events are right-censored.
[2]HR (macitentan relative to standard of care) is from Cox proportional hazards model adjusted for ongoing/planned ERA treatment (yes or no) and WHO FC (I/II vs III) at randomization.
[3]Two-sided p-value from stratified log-rank test. The p-value is for informative purpose only and not for formal hypothesis testing.

[4]HR (macitentan relative to standard of care.) is from unadjusted Cox proportional hazards model.
[5]Two-sided p-value from unstratified log-rank test. The p-value is for informative purpose only and not for formal hypothesis testing.
Source: Reviewer generated analysis based on Applicant submitted data; adtte.xpt

Figure 8. Kaplan Meier Plot: Disease Progression Event-Free Survival in FAS1



FAS1 = Full Analysis Set 1
Two-sided p-value based on the stratified log-rank test for the comparison of matitentan vs SoC
Source: Reviewer analysis using Applicant submitted data; adtte.xpt

Secondary Endpoint – Time to First CEC-Confirmed Hospitalization for PAH

The primary analysis result for the secondary endpoint – time to first CEC-confirmed hospitalization for PAH is shown in **Table 23**.

Figure 9 shows the stratified KM plot for the FAS1 population with stratification factors of WHO functional class (I/II vs III) and ongoing/planned ERA treatment (yes or no) at randomization.

The statistical reviewer's results are close to the Applicant's results for the time to first –CEC-

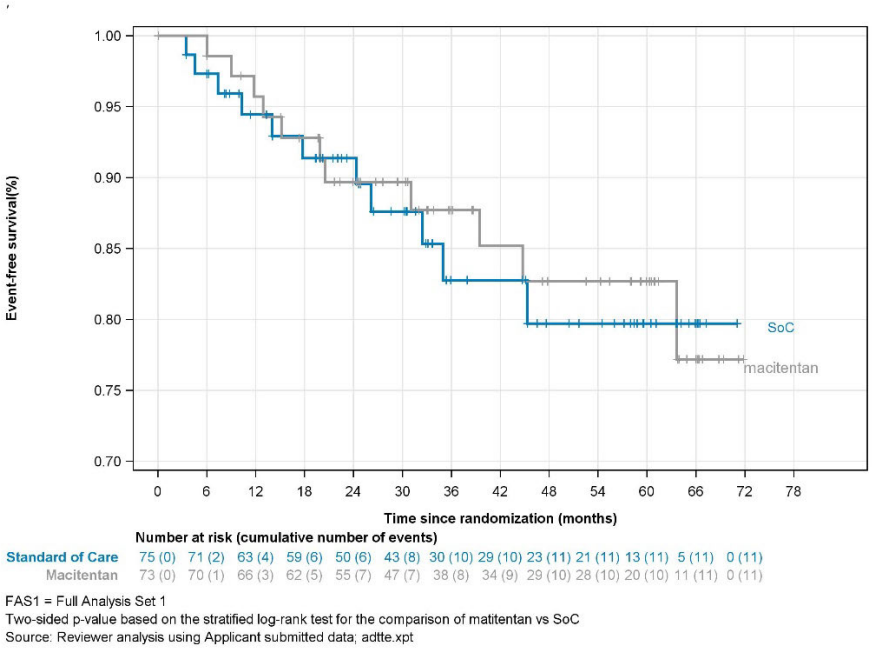
confirmed hospitalization for PAH. There were 22 events total, with the same number of events (11) occurring in each arm. The stratified and unstratified HRs are 0.91(95% CI: (0.39, 2.1)) to 0.94 (95% CI: (0.4, 2.18)), respectively. Overall, there were few events and the wide confidence intervals around the HRs, which cross 1, indicate that the results are inconclusive.

Table 23. Secondary Analysis: Time to First CEC-Confirmed Hospitalization for PAH in FAS1

Time to First Hospitalization or Death for PAH	Macitentan N=73	Standard of Care N=75
Events,[1] n (%)	11 (15.1)	11 (14.7)
Death with No Hospitalization for Worsening PAH, n	6	7
Hospitalization due to PAH, n	5	4
HR[2] (95% CI) (stratified)	0.94 (0.40, 2.18)	-
p-value[3] (stratified)	0.88	-
HR[4] (95% CI) (unstratified)	0.91 (0.39, 2.10)	-
p-value[5] (unstratified)	0.82	-

Abbreviations: CI = confidence interval, HR = hazard ratio, FAS1 = Full Analysis Set 1, n/N = number of patients
[1]Incluce all participants ongoing in the study at the time of cutoff. For those who do not have events are right-censored.
[2]HR (macitentan relative to standard of care) is from Cox proportional hazards model adjusted for ongoing/planned ERA treatment (yes or no) and WHO FC (I/II vs III) at randomization.
[3]Two-sided p-value from stratified log-rank test. The p-value is for informative purpose only and not for formal hypothesis testing.
[4]HR (macitentan relative to standard of care.) is from unadjusted Cox proportional hazards model.
[5]Two-sided p-value from unstratified log-rank test. The p-value is for informative purpose only and not for formal hypothesis testing.
Source: Reviewer generated analysis based on Applicant submitted data; adtte.xpt

Figure 9. Kaplan Meier Plot: First Hospitalization Event-Free Survival in FAS1



FAS1 = Full Analysis Set 1
Two-sided p-value based on the stratified log-rank test for the comparison of matitentan vs SoC
Source: Reviewer analysis using Applicant submitted data; adtte.xpt

Secondary Endpoint – Time to CEC-Confirmed Death Due to PAH

The primary analysis result for the secondary endpoint – time to CEC-confirmed death due to PAH is shown in **Table 24**. The stratified HR is from a Cox proportional hazard ratio model adjusted for the stratification factors of WHO functional class (I/II vs III) and ongoing/planned ERA treatment (yes or no). The adjusted p-value is from the log-rank test stratified by the stratification factors. Unstratified HR and p-values are also presented using the same methods as stratified estimates.

Figure 10 shows the stratified KM plot for the FAS1 population with stratification factors WHO functional class (I/II vs III) and ongoing/planned ERA treatment (yes or no) at randomization.

The statistical reviewer's results are close to the Applicant's results. There were 10 deaths due to PAH events, including 6 and 4 in the macitentan and SoC arms, respectively. The stratified and unstratified HRs are 1.44 (95% CI: (0.41, 5.11)) and 1.5 (95% CI: (0.42, 5.38)), respectively. Although the point estimates of the HRs are numerically greater than 1 (i.e., favor the SoC arm), there were few events and the wide confidence intervals around the HRs indicate that the results are inconclusive.

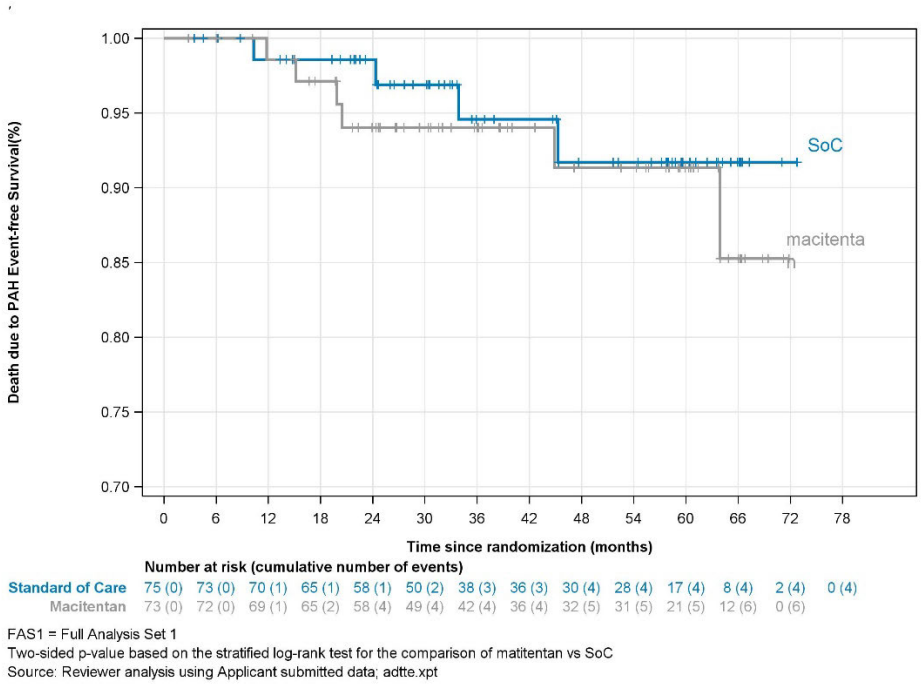
Table 24. Secondary Analysis: Time to CEC-Confirmed Death due to PAH in FAS1

Time to Death due to PAH	Macitentan N=73	Standard of Care N=75
Events,[1] n (%)	6 (8.2)	4 (5.3)
HR[2] (95% CI) (stratified)	1.50 (0.42, 5.38)	-
p-value[3] (stratified)	0.53	-
HR[4] (95% CI) (unstratified)	1.44 (0.41, 5.11)	-
p-value[5] (unstratified)	0.57	-

Abbreviations: CI = confidence interval, HR = hazard ratio, FAS1 = Full Analysis Set 1, n/N = number of patients
[1]Incluce all participants ongoing in the study at the time of cutoff. For those who do not have events are right-censored.
[2]HR (macitentan relative to standard of care) is from Cox proportional hazards model adjusted for ongoing/planned ERA treatment (yes or no) and WHO FC (I/II vs III) at randomization.
[3]Two-sided p-value from stratified log-rank test. The p-value is for informative purpose only and not for formal hypothesis testing.

[4]HR (macitentan relative to standard of care.) is from unadjusted Cox proportional hazards model.
[5]Two-sided p-value from unstratified log-rank test. The p-value is for informative purpose only and not for formal hypothesis testing.
Source: Reviewer generated analysis based on Applicant submitted data; adtte.xpt

Figure 10. Kaplan Meier Plot – Death due to PAH Event-Free Survival in FAS1



FAS1 = Full Analysis Set 1
Two-sided p-value based on the stratified log-rank test for the comparison of matitentan vs SoC
Source: Reviewer analysis using Applicant submitted data; adtte.xpt

Secondary Efficacy Endpoint – Time to All-Cause Deaths from Randomization to Study Closure

The primary analysis result for the secondary endpoint – time to all-cause death is shown in **Table 25**.

Figure 11 includes the stratified KM plot for the FAS1 population with stratification factors WHO functional class (I/II vs III) and ongoing/planned ERA treatment (yes or no) at randomization.

The statistical reviewer's results are close to the Applicant's results. There were 13 death events, including 7 and 6 in the macitentan and SoC arms, respectively. The stratified and unstratified HRs are 1.13 (95%CI: (0.38, 3.37)) and 1.15 (95%CI: (0.38, 3.46)), respectively. Again, , the confidence intervals around these HRs are wide and cross 1, indicating that the results are inconclusive.

Table 25. Secondary Analysis: Time to All-Cause in FAS1

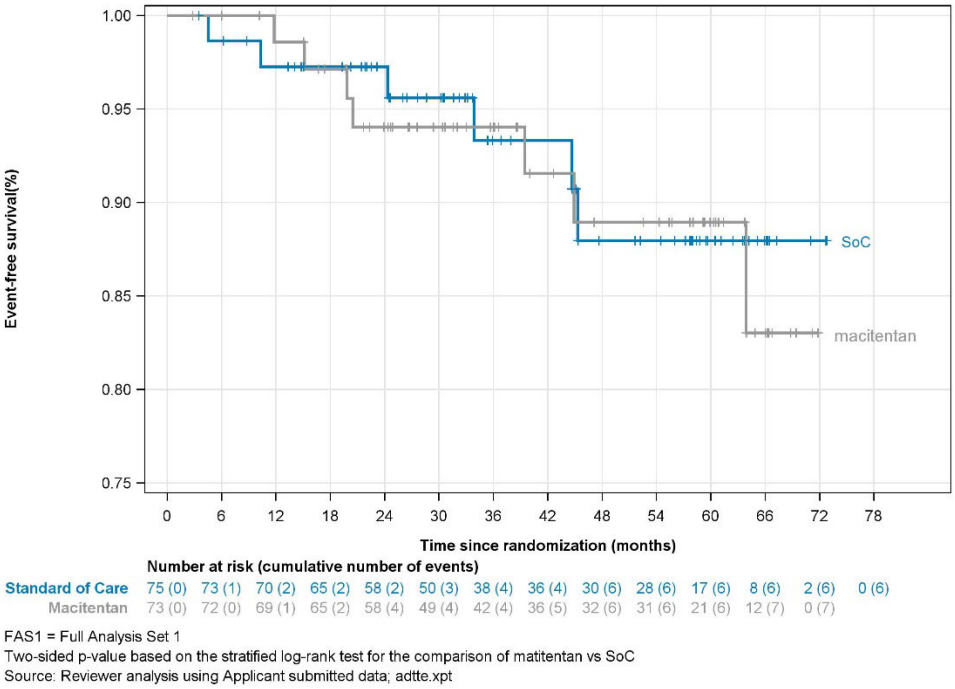
Time to All-Cause Death	Macitentan N=73	Standard of Care N=75
Events,[1] n (%)	7 (9.6)	6 (8.0)
HR[2] (95% CI) (stratified)	1.15 (0.38, 3.46)	-

Time to All-Cause Death	Macitentan N=73	Standard of Care N=75
p-value[3] (stratified)	0.80	-
HR[4] (95% CI) (unstratified)	1.13 (0.38, 3.37)	-
p-value[5] (unstratified)	0.83	-

Abbreviations: CI = confidence interval, HR = hazard ratio, FAS1 = Full Analysis Set 1, n/N = number of patients
[1]Incluce all participants ongoing in the study at the time of cutoff. For those who do not have events are right-censored.
[2]HR (macitentan relative to standard of care) is from Cox proportional hazards model adjusted for ongoing/planned ERA treatment (yes or no) and WHO FC (I/II vs III) at randomization.
[3]Two-sided p-value from stratified log-rank test. The p-value is for informative purpose only and not for formal hypothesis testing.

[4]HR (macitentan relative to standard of care.) is from unadjusted Cox proportional hazards model.
[5]Two-sided p-value from unstratified log-rank test. The p-value is for informative purpose only and not for formal hypothesis testing.
Source: Reviewer generated analysis based on Applicant submitted data; adtte.xpt

Figure 11. Kaplan Meier Plot – All-Causes Death Event-Free Survival in FAS1



FAS1 = Full Analysis Set 1
Two-sided p-value based on the stratified log-rank test for the comparison of matitentan vs SoC
Source: Reviewer analysis using Applicant submitted data; adtte.xpt

Secondary Endpoint - WHO Functional Class Status at Week 12 and 24

The proportion of participants ≥2 years with WHO FC I or II at Week 12 and at Week 24 is shown in **Table 26**. Note that both macitentan and SoC arms had 60 patients with WHO FC I or II at baseline, which accounted for 82% and 80% of randomized subjects in the macitentan and SoC arms, respectively.

Although the stratified odds ratios at Weeks 12 and 24 numerically favor the macitentan arm, the wide confidence intervals indicate the considerable uncertainty surrounding these estimates. In analyses in which the missing WHO FC values at Week 12 are imputed as class III and I in the

macitentan and SoC arms, respectively, the stratified odds ratio for Week 12 is 2.43 (95% CI (0.59, 10.02)). When the same imputation method is applied to the missing WHO FC values at Week 24, the stratified odds ratio for Week 24 is 1.91 (95% CI (0.50, 7.27)). In summary, these analyses indicate that using an imputation method that is the least favorable one to the macitentan arm produces results that are largely consistent with the results of the primary analysis and that missing data (2.7% in the macitentan arm and 5.3% in the SoC arm) does not have a significant impact on the analysis results.

Table 26. WHO Functional Class I or II (Yes vs No) Up to End of Randomized in FAS1

WHO FC Status at Baseline, Week and 24	Macitentan N=73	Standard of Care N=75
Baseline		
n/N[1] (%)	60/73 (82.2)	60/75 (80.0)
Week 12		
n/N[1] (%)	63/71(88.7)	58/71 (81.7)
Stratified Odds Ratio[2,3]	4.64	-
95% CI for Odds Ratio	(0.829, 25.91)	-
Week 24		
n/N[1] (%)	63/70(90)	52/63 (82.5)
Stratified Odds Ratio[2,3]	6.42	-
95% CI for Odds Ratio	(1.107, 37.164)	-

Abbreviations: CI = confidence interval, FAS1 = Full Analysis Set 1, n/N = number of participants, WHO =World Health Organization
[1] n = number of subjects with WHO FC I or II; N= total number of subjects with a WHO FC value.
[2] Odds ratio and confidence limit calculated using logistic regression adjusted for ongoing/planned ERA treatment (yes or no) and WHO FC (I/II vs III) at randomization.
[3] In case of missing Week 12 values, subjects who are hospitalized due to PAH (CEC confirmed) or died prior to or at Week 12, the value of WHO FC will be imputed as the worst case (e.g., IV) at Week 12. The same imputation rule is applied for subjects who are hospitalized due to PAH (CEC confirmed) or died prior to or at Week 24, but imputing the worst case at Week 24.
Source: Applicant's Result; Table 26, page 101, AC-055-312, CSR End of Core Period; the results were validated by the reviewer.

Secondary Endpoint - Percent of Baseline plasma NT-proBNP at Weeks 12 and 24

The MMRM analysis result for the percent of baseline in NT-proBNP at Weeks 12 and 24 is shown in **Table 27**. The mean absolute change with +/- SE change from baseline in NT-proBNP (pmol/L) over time is shown in **Table 27**. Note that after Week 48, only the time points with at least 10% of participants in the macitentan arm who have valid NT-proBNP values are displayed.

The MMRM model assumes missing data are missing at random, which is not an appropriate assumption; the reason the data are missing must be considered (e.g., data that are missing because of lack of treatment effect are not missing at random). Given the amount of missing data (> 12 % in both arms), the analysis results shown in **Table 27** and **Figure 12** are not considered to be

interpretable.

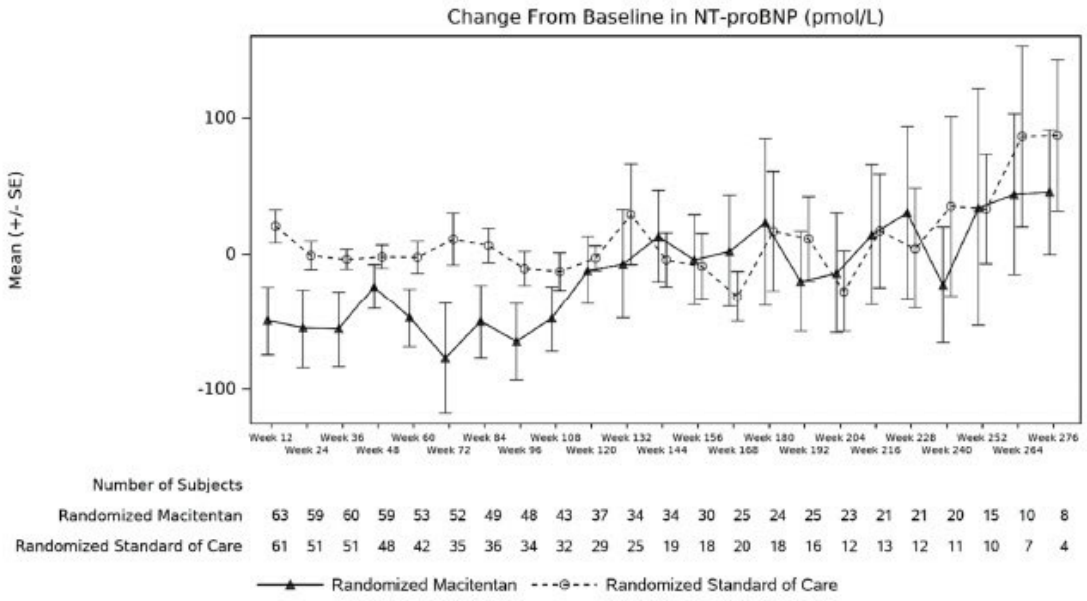
Table 27. Percent of Baseline NT-proBNP (pmol/L) Up to End of Randomized in FAS1

	Randomized Macitentan	Randomized Standard of Care
Analysis set: FAS1	73	75
Percent of Baseline NT-proBNP		
Repeated measures mixed model[a]		
Number of subjects included in the analysis[b]	64	65
Week 12		
Geometric LS Mean	0.72	1.01
95% CI of geometric LS Mean	(0.54; 0.98)	(0.75; 1.36)
Geometric LS Means ratio	0.72	
95% CI for geometric LS Means ratio	(0.49; 1.05)	
2-sided p-value	0.086	
Week 24		
Geometric LS Mean	0.76	0.78
95% CI of geometric LS Mean	(0.56; 1.03)	(0.57; 1.07)
Geometric LS Means ratio	0.97	
95% CI for geometric LS Means ratio	(0.66; 1.43)	
2-sided p-value	0.884	
Overall treatment effect[c]		
Geometric LS Mean	0.75	0.86
95% CI of geometric LS Mean	(0.58; 0.96)	(0.66; 1.12)
Geometric LS Means ratio	0.86	
95% CI for geometric LS Means ratio	(0.64; 1.16)	
2-sided p-value	0.333	
Treatment-by-visit interaction p-value	0.258	

[a] Repeated measures mixed model on log-transformed NT-proBNP values.
[b] The subjects included in the analysis are those with baseline and at least one post-baseline value.
The model includes randomized treatment, visit, treatment by visit interaction, the 2 stratification factors and baseline value as fixed effects, and subject as random effect.
[c] The overall treatment effect is estimated using the same model excluding the treatment by visit interaction factor.
Note: After Week 48 only timepoints with a corresponding value in at least 10% of the subjects in the Macitentan arm are displayed.
The treatment effect expressed as geometric means ratio and its associated 95% CI is estimated by inversely transforming the difference in change from baseline between treatment groups and the associated 95% CI, both estimated from the repeated measures mixed model on the log-transformed NT-proBNP values.
Covariance matrix TOEP is used.

Source: Applicant's Result; Table 27, page 102, AC-055-312, CSR End of Core Period

Figure 12. Change From Baseline in NT-proBNP Over Time in FAS1



Key: NT-proBNP = N-terminal prohormone of brain natriuretic peptide; SE = Standard error.
Note: After Week 48 only timepoints with a corresponding value in at least 10% of the subjects in the Macitentan arm are displayed.

Source: Applicant's Result; Figure 9, page 103, AC-055-312, CSR End of Core Period

The Applicant's results for endpoints derived from accelerometry, echocardiography and PedsQL™ are presented in section 15. Analyses did not suggest a treatment effect on these endpoints.

7. Safety

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

See Pharmacology/Toxicology review for NDA 204410 by Dr. William Link (08/26/2013) in DARRTs. The OPSUMIT label contains a boxed warning for embryo-fetal toxicity. For all female patients, macitentan is available only through a restricted program called the Macitentan-Containing Products Risk Evaluation and Mitigation Strategy.

7.2. Safety Concerns Based on Drug Class

To date, FDA has approved 5 ERAs. Ambrisentan, bosentan, and macitentan are approved for PAH. Aprocitentan and sparsentan are approved for hypertension and primary immunoglobulin A nephropathy, respectively.

Labeling for all five agents includes a boxed warning for embryo-fetal toxicity and all five agents are only available through a REMS program because of this risk; bosentan and sparsentan also have a boxed warning and associated REMS for the risk of hepatotoxicity. The Warnings and Precautions section of labeling for these agents generally include the following risks: embryo-fetal toxicity, decreased sperm counts, decreases in hemoglobin and hematocrit, and fluid retention; labeling for bosentan, macitentan, aprocitentan, and sparsentan also contain a Warning and Precaution for hepatotoxicity.

7.3. Safety Concerns Identified Through Postmarket Experience

The Applicant submitted an ad hoc report, Description of Cumulative Postmarketing Cases Reporting Off-Label Macitentan Use in Pediatric Patients (up to October 17, 2023) that provides a summary of safety information from the GMS global safety database on the off-label use, including doses reported, of macitentan 10 mg tablet in children below 18 years of age.

From 18 October 2013 until 17 October 2023, a search retrieved 202 cases (127 nonserious, 75 serious) reported in participants under 2 years of age, reporting a total of 679 events; 476 cases (320 nonserious, 156 serious) in patients from 2 to below 12 years of age, reporting a total of 1,498 events and 615 cases (310 nonserious, 305 serious) in patients from 12 to below 18 years of age, reporting a total of 2,461 events.

The reported AEs were consistent with the known safety profile of macitentan. No new safety signals were identified.

7.4. FDA Approach to the Safety Review

FDA's safety review focused on treatment-emergent AEs in the safety population in the TOMORROW study. The safety population included all subjects who received at least 1 dose of study treatment and analyzed based on actual treatment received. All AEs were coded using MedDRA version 26.1.

Clinical trial data are for the most part presented from the Applicant's CSR End of Core Period — a limited independent safety analysis was conducted since the Applicant is not seeking an indication for the treatment of pediatric PAH and no safety data are proposed for inclusion in labeling. The Clinical Reviewer performed a MAED analysis of AEs and SAEs using the narrow Office of New Drug's custom medical query (OCMQ) and MedDRA's system of organ class (SOC).

FDA evaluated the data quality and integrity and found no issues with the clinical datasets.

FDA also reviewed the 120-day safety update that was submitted on December 9, 2024.

7.5. Adequacy of the Clinical Safety Database

The size of the safety database is considered adequate to characterize safety given the rarity of the disease in children and well-established safety profile in adults.

In subjects ≥2 years, the total exposure to macitentan is 253 person-years with a median duration of exposure of 168 weeks (**Table 28**). Treatment duration was longer for subjects in the macitentan arm compared to the SoC arm (188 person-years), consistent with the greater number of subjects discontinuing treatment in the SoC as compared to macitentan arm (**Table 19**).

Treatment duration for the 9 participants <2 years ranged from 7 to 73 weeks. Median duration of treatment was 37 weeks.

Table 28. Duration of Randomized Treatment for Subjects ≥2 Years

	Randomized Macitentan	Randomized Standard of Care
Analysis set: SAS1	72	75
Duration of study treatment (Weeks)		
N	72	75
Mean (SD)	183.36 (87.121)	130.59 (93.102)
Median	168.43	115.00
Range	(12.9; 312.4)	(0.1; 316.4)
Cumulative duration of study treatment		
N	72	75
At least 3 months	71 (98.6%)	69 (92.0%)
At least 6 months	68 (94.4%)	66 (88.0%)
At least 12 months	66 (91.7%)	58 (77.3%)
At least 18 months	64 (88.9%)	46 (61.3%)
At least 24 months	58 (80.6%)	41 (54.7%)
At least 30 months	49 (68.1%)	36 (48.0%)
At least 36 months	42 (58.3%)	24 (32.0%)
At least 42 months	35 (48.6%)	22 (29.3%)
At least 48 months	31 (43.1%)	18 (24.0%)
At least 54 months	29 (40.3%)	16 (21.3%)
At least 60 months	20 (27.8%)	10 (13.3%)
At least 66 months	10 (13.9%)	4 (5.3%)
At least 72 months	0	1 (1.3%)
Subject year exposure[a]		
N	72	75
Exposure (years)	253.0	187.7

Source: Table 12, AC-055-312, CSR End of Core Period

A total of 96 subjects entered the Single Arm Extension Period (SAEP). At the time of the 120-day safety update, 3 subjects discontinued macitentan treatment and withdrew from the study. Reasons for termination included death, lost to follow-up and withdrawal of consent.

7.6. Safety Results

7.6.1. TOMORROW Safety Results

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary

The incidence of AEs, SAEs and AEs leading to discontinuation of treatment was higher in the macitentan arm compared to the SoC arm in the main treatment period and in the overall core period (**Table 29**). When comparing the exposure-adjusted incidence rate in the main treatment period, the AE rates between treatment arms is similar: 26.5 person-years for macitentan and 27.2 person-years for SoC.

Table 29. Overview of Treatment-Emergent Adverse Events in Main Treatment Period

	Main treatment period[1]		Overall core period[2]	
	Randomized Macitentan	Randomized Standard of Care	Randomized Macitentan	Randomized Standard of Care
Analysis set: SAS1	72	75	72	75
Subjects with 1 or more:				
AEs	67 (93.1%)	51 (68.0%)	67 (93.1%)	57 (76.0%)
Macitentan related AEs [a]	15 (20.8%)	NA	15 (20.8%)	1 (1.3%)
Serious AEs	26 (36.1%)	16 (21.3%)	26 (36.1%)	21 (28.0%)
Macitentan related serious AEs	2 (2.8%)	NA	2 (2.8%)	0
AEs leading to premature discontinuation of randomized macitentan or SoC	4 (5.6%)	2 (2.7%)	4 (5.6%)	2 (2.7%)
Macitentan related AEs leading to premature discontinuation of macitentan [a]	4 (5.6%)	NA	4 (5.6%)	0
AEs leading to death [b]	0	1 (1.3%)	0	2 (2.7%)
Macitentan related AEs leading to death [b]	0	NA	0	0
COVID-19 associated AEs [c]	12 (16.7%)	8 (10.7%)	12 (16.7%)	11 (14.7%)

Key: AE = Adverse event; EOCP = End of core period; NA = Not applicable; SoC = Standard of care.
[a] An AE is assessed by the investigator as related to study agent.
[b] AEs leading to death are based on AE outcome of Fatal.
[c] COVID-19 associated AEs are based on events that code to a COVID-19 MedDRA term.
[1] Main treatment period: from randomization up to end of randomized macitentan or SoC + 30 days (or EOCP, whichever comes first), or for crossover subjects up to start of macitentan or end of SoC + 30 days, whichever comes first.
[2] Overall core period: from randomization up to EOCP. It might include crossover data.
Note: Only AEs with onset date occurring during the period under consideration are included.
[tsfae01.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_cco5/tsfae01.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-28 ; Production Date: 07MAR2024, 08:35

Source: Table 41, AC-055-312, CSR End of Core Period

7.6.1.2. Deaths

Thirteen deaths occurred in TOMORROW: 7 deaths in the macitentan arm and 6 deaths in the SoC arm. None of the deaths occurred in subjects <2 years. Causes of death are presented in **Table 30**. The CEC confirmed that 6 deaths in the macitentan arm and 4 deaths in the SoC arm were due to PAH disease progression.

Two deaths were reported as AEs with fatal outcome in the SoC arm: a COVID-19 death and one due to hypoxic-ischaemic encephalopathy.

Table 30. Primary Cause of Death; SAS1 Population

	Randomized Macitentan	Randomized Standard of Care
Analysis set: SAS1	72	75
Primary cause of death	7 (9.7%)	6 (8.0%)
PULMONARY ARTERIAL HYPERTENSION	2 (2.8%)	0
CARDIAC FAILURE ACUTE	1 (1.4%)	0
CARDIAC FAILURE CONGESTIVE	1 (1.4%)	0
HYPERTROPHIC CARDIOMYOPATHY	1 (1.4%)	0
MYOCARDIAL INFARCTION	1 (1.4%)	0
RIGHT VENTRICULAR FAILURE	1 (1.4%)	0
COVID-19 PNEUMONIA	0	1 (1.3%)
DEATH	0	2 (2.7%)
HYPOXIC-ISCHAEMIC ENCEPHALOPATHY	0	1 (1.3%)
PULMONARY HYPERTENSIVE CRISIS	0	1 (1.3%)
SUDDEN DEATH	0	1 (1.3%)

Note: The cause of death is based on the Death eCRF.

[tsfdth01.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_cco5/tsfdth01.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-28 ; Production Date: 07MAR2024, 08:35

Source: Table 50, AC-055-312, CSR End of Core Period

There was 1 additional death reported in the 120-day safety update. A 12-year-old subject who had iPAH and WHO FC II at baseline experienced worsening of PAH during the core period while on SoC (bosentan and sildenafil). At the start of SAEP, the subject switched from bosentan to macitentan and continued treatment until death due to visceral congestion on SAEP Day 193.

7.6.1.3. Serious Treatment-Emergent Adverse Events

SAEs by nOCMQ in participants ≥2 years (excluding disease progression events) are summarized in **Table 31**. SAEs by PT reported in more than 1 subject in the macitentan arm were pneumonia (n=5), gastritis (n=2), non-cardiac chest pain (n=2), urinary tract infection (n=2) and anemia (n=2). More subjects in the macitentan arm had SAEs that fell within the Infections and Infestations SOC; however, there was no imbalance in these SAEs when adjusted for exposure duration (4.3 per 100 person-years for macitentan *vs*. 3.7 per 100 person-years for SoC).

SAEs were reported for 4 participants <2 years. Pneumonia (PT) was the only SAE reported in more than 1 subject.

Table 31. Subjects ≥2 Years with Serious Treatment-Emergent Adverse Events by Narrow OCMQ with Risk Difference >2%

	MACITENTAN (N = 72) 253 person-years			STANDARD OF CARE (N = 75) 188 person-years			
SOC nOCMQ	Events	Number of Subjects	Proportion (%)	Events	Number of Subjects	Proportion (%)	Risk Difference
Infection and Infestation		***11***	***15.3***		***7***	***9.3***	***6.0***
Bacterial Infection	6	6	8.3	0	0	0	8.3
Pneumonia	7	6	8.3	1	1	1.3	7
Renal and Urinary Tract Infection	2	2	2.8	0	0	0	2.8
Cardiac Disorders		***4***	***5.6***		***2***	***2.7***	***2.9***
Arrhythmia	3	2	2.8	0	0	0	2.8
Tachycardia	3	2	2.8	0	0	0	2.8
Respiratory, thoracic and mediastinal disorders		***4***	***5.6***		***3***	***4.0***	***1.6***
Bronchospasm	4	2	2.8	0	0	0	2.8

Abbreviations: OCMQ, OND custom medical query; nOCMQ, narrow OCMQ; SOC, system of organ class

Source: Reviewer's MAED analysis using adsl.xpt and adae.xpt

As of the 120-day safety cut-off date, there were 10 subjects with at least 1 SAE in the SAEP. The only SAE reported in more than 1 subject was pneumonia (n=3). Except for the subject who died of visceral congestion, no other SAE led to permanent discontinuation of macitentan.

7.6.1.4. Adverse Events Leading to Treatment Discontinuation

AEs leading to premature discontinuation of study treatment in participants ≥2 years are summarized in **Table 32**. No participants <2 years prematurely discontinued study treatment due to an AE.

Table 32. Subject ≥ 2Years With Adverse Events[1] Leading to Treatment Discontinuation by System Organ Class and Preferred Term

	Randomized Macitentan	Randomized Standard of Care
Analysis set: SAS1	72	75
Subjects with 1 or more AEs	4 (5.6%)	2 (2.7%)
System organ class Preferred term		
Investigations	2 (2.8%)	0
Alanine aminotransferase increased	1 (1.4%)	0
Transaminases increased	1 (1.4%)	0
Blood and lymphatic system disorders	1 (1.4%)	0
Anaemia	1 (1.4%)	0
Nervous system disorders	1 (1.4%)	0
Headache	1 (1.4%)	0
Cardiac disorders	0	1 (1.3%)
Cardiac arrest	0	1 (1.3%)
Eye disorders	0	1 (1.3%)
Eye swelling	0	1 (1.3%)
Ocular hyperaemia	0	1 (1.3%)
Gastrointestinal disorders	0	1 (1.3%)
Abdominal pain upper	0	1 (1.3%)
Faeces discoloured	0	1 (1.3%)
Vomiting	0	1 (1.3%)

Key: AE = Adverse event; EOCP = End of core period; SoC = Standard of care.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 26.1.
Only AEs with onset date occurring during the period under consideration are included.
Main treatment period: from randomization up to end of randomized macitentan or SoC + 30 days (or EOCP, whichever comes first), or for crossover subjects up to start of macitentan or end of SoC + 30 days, whichever comes first.
[tsfae06.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_cco5/tsfae06.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-28 ; Production Date: 07MAR2024, 08:35

Source: Table 56, AC-055-312 CSR End of Core Period

As of the 120-day safety cut-off date, 2 participants discontinued study intervention due to pulmonary fibrosis and the other due to visceral congestion in the SAEP.

7.6.1.5. Treatment-Emergent Adverse Events

Higher rates of AEs were reported in the macitentan arm versus the SoC arm during the main treatment period for subjects ≥2 years: 93% of subjects in macitentan arm versus 68% of subjects in the SoC arm (**Table 33**). When adjusted for exposure, there was no imbalances in AEs with a RD greater than 3 per 100 person-years in the macitentan arm.

AEs in subjects <2 years reported for more than 1 subject during the main treatment period were upper respiratory tract infection (4 subjects [44%]), gastroenteritis (3 subjects [33%]), and COVID-19 and pneumonia (2 subjects each [22%]).

Table 33. Patients With Common Treatment-Emergent Adverse Events Occurring at ≥3% Frequency in Macitentan Arm

	MACITENTAN (N = 72; 253 person-years)			STANDARD OF CARE (N = 75; 188 person-years)			MACITENTAN vs. STANDARD OF CARE
Narrow OCMQ	Events	Subjects	(%)	Events	Subjects	(%)	Risk Difference (95% CI)
Nasopharyngitis	88	42	58.3	71	29	38.7	19.7 (3.8, 35.5)
Viral Infection	50	30	41.7	41	18	24	17.7 (2.7, 32.6)
Bacterial Infection	18	13	18.1	8	6	8	10.1 (-0.7, 20.9)
Anemia	20	12	16.7	6	5	6.7	10 (-0.3, 20.3)
Fatigue	8	7	9.7	2	2	2.7	7.1 (-0.7, 14.8)
Pyrexia	18	8	11.1	3	3	4	7.1 (-1.4, 15.6)
Tachycardia	6	5	6.9	0	0	0	6.9 (1.1, 12.8)
Abnormal Uterine Bleeding	8	6	8.3	2	2	2.7	5.7 (-1.7, 13)
Pneumonia	10	7	9.7	3	3	4	5.7 (-2.4, 13.9)
Headache	23	14	19.4	21	11	14.7	4.8 (-7.4, 16.9)
Arrhythmia	5	4	5.6	1	1	1.3	4.2 (-1.7, 10.1)
Cough	16	9	12.5	12	7	9.3	3.2 (-6.9, 13.3)

Abbreviations: OCMQ, OND custom medical query; nOCMQ, narrow OCMQ; SOC, system of organ class

Source: Reviewer's MAED analysis using adsl.xpt and adae.xpt

The safety profile of macitentan is well characterized in adult PAH patients. Known adverse reactions are anemia, hepatic disorders, hypotension, symptomatic hypotension, and edema/fluid retention. The incidence of these AEs of special interest in subjects ≥2 years is shown in **Table 34**. No AE of special interest occurred in subjects <2 years. These finding appear, as a whole, to be consistent with those seen in adults.

Table 34. Subjects ≥ 2 Years with Treatment-Emergent Adverse Events of Special Interest

	Randomized Macitentan	Randomized Standard of Care
Analysis set: SAS1	72	75
Subjects with 1 or more AEs	18 (25.0%)	7 (9.3%)
AESI category Preferred term		
Anemia	11 (15.3%)	2 (2.7%)
Anaemia	7 (9.7%)	1 (1.3%)
Haemoglobin decreased	4 (5.6%)	0
Iron deficiency anaemia	1 (1.4%)	1 (1.3%)
Edema and fluid retention	4 (5.6%)	1 (1.3%)
Oedema peripheral	1 (1.4%)	1 (1.3%)
Pericardial effusion	1 (1.4%)	0
Pleural effusion	1 (1.4%)	0
Pulmonary oedema	1 (1.4%)	0
Hepatic disorders	3 (4.2%)	3 (4.0%)
Alanine aminotransferase increased	2 (2.8%)	3 (4.0%)
Aspartate aminotransferase increased	1 (1.4%)	0
Transaminases increased	1 (1.4%)	0
Hypotension	3 (4.2%)	1 (1.3%)
Hypotension	2 (2.8%)	1 (1.3%)
Orthostatic hypotension	1 (1.4%)	0
Symptomatic Hypotension	0	0

Key: AE = adverse event; EOCP = End of core period; SoC = Standard of care.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 26.1.
Only AEs with onset date occurring during the period under consideration are included.
Main treatment period: from randomization up to end of randomized macitentan or SoC + 30 days (or EOCP, whichever comes first), or for crossover subjects up to start of macitentan or end of SoC + 30 days, whichever comes first.
[tsfaesi01.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_cco5/tsfaesi01.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-28 ; Production Date: 07MAR2024, 08:40

Source: Table 58, AC-055-312, CSR End of Core Period

As of the 120-day safety cut-off date, 4 subjects had 1 or more AESI: 3 subjects had increased liver enzymes, 1 subject had iron deficiency anemia and 1 subject had pericardial effusion. No subject met criteria for Hy's law.

Three of the 4 subjects with AESIs received macitentan during the core period.

7.6.1.6. Laboratory Findings

Liver Function Tests

Increases in hepatic enzymes are a known adverse reaction and the OPSUMIT USPI carries a warning for hepatotoxicity.

Elevated ALT and/or AST of >3×ULN and TBIL >2×ULN reported in subjects ≥2 years based on central and local laboratories are shown in **Table 35**. A brief overview of these cases is provided below.

- Subject (b) (6) in the SoC arm (PAH specific therapy of sildenafil 12.5 mg BID) met the biochemical criteria for Hy's Law case (ALT and/or AST >3 ULN + TBIL >2 ULN + AP <2 ULN). These elevations occurred in the context of non-alcoholism like disease with increased fatty content in the liver in an overweight participant. No action was taken with the SoC treatment.
- Two subjects with an ALT > 8 x ULN in the macitentan arm were discontinued from treatment. Neither subject had TBIL >2 ULN at the same occurrence of the elevated ALT levels.
  - Subject (b) (6) had an ALT >8 x ULN that was serious, of severe intensity, considered related to macitentan, resulted in drug withdrawal, and was reported as recovered/resolved. This event occurred in the context of right heart failure and respiratory tract infection.
  - Subject (b) (6) had an ALT >8 x ULN that was not serious, of mild intensity, considered related to macitentan, resulted in drug withdrawal, and was reported as recovered/resolved.

Table 35. Elevated Liver Enzyme Tests Based on Central and Local Laboratories for Subjects ≥2 Years

	Randomized Macitentan	Randomized Standard of Care
Analysis set: SAS1	72	75
N	72	71
ALT > 3 ULN at any time	2 (2.8%)	3 (4.2%)
ALT and/or AST > 3 ULN at any time	2 (2.8%)	3 (4.2%)
ALT > 5 ULN at any time	2 (2.8%)	0
ALT and/or AST > 5 ULN at any time	2 (2.8%)	0
ALT > 8 ULN at any time	2 (2.8%)	0
ALT and/or AST > 8 ULN at any time	2 (2.8%)	0
ALT and/or AST > 3 ULN + TBIL > 2 ULN at any time	0	1 (1.4%)
ALT and/or AST > 3 ULN + TBIL > 2 ULN at the same time	0	1 (1.4%)
ALT and/or AST > 3 ULN + TBIL > 2 ULN + AP < 2 ULN at the same time	0	1 (1.4%)
TBIL > 2 ULN at any time	5 (6.9%)	1 (1.4%)

Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; AP = alkaline phosphatase; EOCP = End of core period; SoC = Standard of care; TBIL = total bilirubin; ULN = upper limit of normal.
Note: The number of percent of subjects with the applicable condition for at least one visit post-baseline visit, where the same condition was not met at baseline is displayed.
Main treatment period: from randomization up to end of randomized macitentan or SoC + 30 days (or EOCP, whichever comes first), or for crossover subjects up to start of macitentan or end of SoC + 30 days, whichever comes first.
Adapted from Attachment TSFLAB01PH, refer to Section 3.7.4

Source: Table 60 AC-055-312, CSR End of Core Period

Hematology

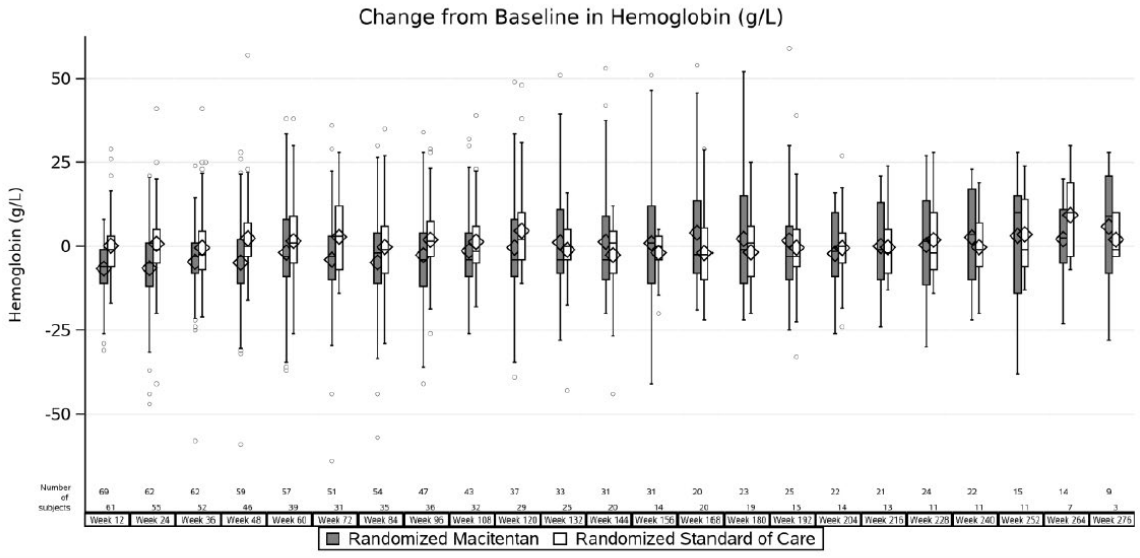
Decrease in hemoglobin is a known adverse reaction and the OPSUMIT USPI carries a warning for decreases in hemoglobin.

In subjects ≥ 2 years, mean change from baseline in hemoglobin up to Week 96 was in the range of -1.9 to -6.6 g/L (**Figure 13**). No trends over time in decrease from baseline in hematology values were observed in the SoC arm.

No trends over time in change from baseline in hematology values were observed in participants <2 years.

Figure 13. Change From Baseline in Hemoglobin for Subjects ≥ 2 Years

GSFLAB01a: Box Plot of Change From Baseline in Hemoglobin Up to End of Randomized Macitentan or SoC + 30 Days, or Up to Start of Macitentan for Crossover Subjects for Subjects ≥ 2 Years Old; SAS1 Analysis Set (Study AC-055-312)



Key: SoC = Standard of care.
Note: The line inside the box represents the median value. The symbol inside the box represents the mean value. The outer box borders represent the first and third quartiles. The upper and lower whiskers represent the location of the maximum and minimum within the first and third quartiles +/- 1.5 times the interquartile range. The circle represents any outliers.
After Week 48 only timepoints with a corresponding value in at least 10% of the subjects in the Macitentan arm are displayed.
[gsflab01a.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_cco5/gsflab01a.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-28 ; Production Date: 13MAR2024, 01:42

Source: Figure GSFLAB01a, AC-055-312 CSR End of Core Period

7.6.1.7. Vital-Sign Analyses

Change from baseline in vital signs (diastolic blood pressure, systolic blood pressure, and heart rate) in subjects ≥2 years was similar between macitentan and SoC arms at the majority of timepoints. Change from baseline in vital signs in subjects <2 years was not significant.

8. Therapeutic Individualization

8.1. Intrinsic Factors

No dedicated evaluation of other intrinsic factors besides age (i.e., pediatrics) was conducted.

8.2. Extrinsic Factors

No dedicated evaluation of extrinsic factors was conducted.

8.3. Plans for Pediatric Drug Development

Per the Applicant, there are no further studies to evaluate the efficacy and safety of macitentan in pediatric PAH population are planned.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

The OPSUMIT label has a boxed warning for embryo-fetal toxicity. For all female patients, OPSUMIT is available only through a restricted program called the Macitentan-Containing Products Risk Evaluation and Mitigation Strategy.

9. Product Quality

Since the product will not be indicated for the treatment of the pediatric patients with PAH, the dispersible tablets will not be entered into the marketplace.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Clinical site inspections were not recommended because the Applicant is not seeking a pediatric indication because efficacy was not demonstrated and review of the financial disclosures did not raise any concerns about the validity or reliability of the data.

11. Advisory Committee Summary

An Advisory Committee meeting was not held because there were no controversial or challenging

issues that would benefit from advisory committee discussion.

III. Additional Analyses and Information

12. Summary of Regulatory History

- Macitentan was approved on October 18, 2013, for treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression.
- On January 27, 2016, the Agency received Actelion's Proposed Pediatric Study Request (PPSR) dated January 22, 2016, to NDA 204410.
- On April 13, 2016, FDA issued the WR for macitentan.
- On May 3, 2018, Actelion submitted a proposal to amend the WR due date for the final pediatric study reports to October 5, 2024.
- On April 23, 2020, the WR was amended to change the due date for the final pediatric study reports to October 5, 2024.
- At a Type A Meeting on August 4, 2021, the Sponsor discussed proposed changes to the design of Study No. AC-055-312 (TOMORROW) due to slow enrollment and event accrual. The Sponsor also noted that the study was under a Pediatric Investigation Plan (PIP) per the European Medicines Agency (EMA). Specifically, the Sponsor proposed the following changes:
    - Replace the primary endpoint of time to first Clinical Event Committee (CEC)-confirmed disease progression with pharmacokinetic (PK) assessments and
    - Analyze the time to first CEC-confirmed disease progression as a secondary endpoint.
    - Pharmacodynamic (PD) markers (such as World Health Organization functional class [WHO FC] and N-terminal pro-brain natriuretic peptide [NT-proBNP]) and clinical endpoints will be secondary endpoints.
    - There will be two time points of study analysis: an interim analysis in December 2022 and a final analysis in first quarter of 2024.
    - Up to 200 subjects will be enrolled in this study based on current accrual.
- At the August 4, 2021, meeting, the Division stated that (b) (4) [redacted]

[redacted] they were willing to write a modification to the WR if, at the interim analysis, the study demonstrated efficacy on the pre-specified endpoint or on a pre-specified pharmacodynamic biomarker. The Division reiterated that the WR would not be modified until topline results of the interim analysis were available for review.

- On December 8, 2021, the Sponsor submitted a protocol amendment [Version 9; November 23, 2021], which implemented the changes that the Sponsor proposed during the August 4, 2021, meeting, among others.
- At a Type C Meeting on July 21, 2022, the Sponsor discussed its proposed plan [redacted] During the meeting, the Division stated that it had determined that the information provided was not adequate [redacted] The Division also stated that if the Sponsor wanted to seek an amendment to the WR, they would need to have an agreed-upon analysis plan in place for the efficacy endpoint prior to the interim analysis.
- The Sponsor submitted a proposed analysis plan on November 15, 2022, and the Division provided a response in an advice letter sent March 20, 2023. The advice letter stated that (1) the role the proposed alternative hierarchical analyses were expected to play in decision-making were not clear, (2) in the setting of an open-label trial, some of the Sponsor's proposed components were uninterpretable for the assessment of effectiveness, and (3) the Sponsor should enumerate the criteria that would constitute a hospitalization for PAH and a clinical worsening event so their validity could be assessed in that context.
- At a Type A Meeting on June 29, 2023, the Sponsor presented the results of the interim analysis and stated that the results [redacted] The Agency disagreed [redacted] In response to the Sponsor's statement [redacted] the Division stated [redacted] that the efficacy results presented in the interim analysis did not support a modification to the WR. The Division indicated that it

would be willing to look at additional data from the next cut-off point to see if the results were interpretable and useful to inform labeling.

- At a teleconference meeting on June 21, 2024, the Sponsor presented the results from the end of the randomized core period and requested an amendment to the WR. The Division stated that the Sponsor's submitted evidence did not demonstrate nor refute effectiveness or safety for macitentan in the treated population, and that the Division did not agree that data from the TOMORROW study answered any clinical question about the use of macitentan in the pediatric PAH population and therefore the data did not inform labeling. Since the data would not inform labeling, the Division did not believe the WR should be amended.
- On July 12, 2024, the Sponsor submitted correspondence providing its "rationale to justify that [its] pediatric program has been conducted with maximal efforts and has fairly responded to the Written Request."

13. Clinical Pharmacology

13.1. Bioanalytical Method Validation and Performance

For the quantitation of macitentan and its active metabolite, aprocitentan in human plasma, liquid chromatography – tandem mass spectrometry (LC-MS/MS) methods were developed and validated at (b) (4) Actelion (Allschwil, Switzerland), (b) (4) It should be noted that this review focuses on the evaluation of the bioanalytical method validation and performance for the 3 relative BA studies (i.e., AC-055-121, 67896062PAH1008, and 67896062PAH1010) and the Phase 3 trial (i.e., AC-055-312 [TOMORROW]). The dynamic range for both analytes were 1-2,000 ng/mL. Long term stability in human EDTA plasma was established adequately covering the sample storage periods in each study at -20°C. Intra-run and inter-run accuracy and precision were within the recommendations of the Agency's *Guidance for Industry: Bioanalytical Method Validation Guidance* (https://www.fda.gov/media/70858/download). The bioanalytical method validation performance for each method is summarized below.

Table 36. Bioanalytical Method Validation Performance Summary for Method BA13063 at (b) (4) (Used in Studies 67896062PAH1008, 67896062PAH1010, and AC-055-312 [TOMORROW])

BA13063 (b) (4) [Mod5.3.1.4/BA13063]	Macitentan	Aprocitentan
Matrix	plasma	plasma
Validated concentration range	1-2,000 ng/mL	1-2,000 ng/mL
Inter-run accuracy (%)	96.7-99.6	92.6-100.0
Inter-run precision (%CV)	0.0-3.9	1.1-2.5
Intra-run accuracy (%)	93.9-102.8	90.2-101.3
Intra-run precision (%CV)	2.2-5.1	2.7-8.0
Intra-run accuracy (10 x dilution) (%)	n.d.	n.d.
Intra-run precision (10 x dilution) (%CV)	n.d.	n.d.
Incurred sample reproducibility	67896062PAH1006 98.4% of 186 samples within 20% 67896062PAH1008: 97% of 67 samples within 20% 67896062PAH1010: 100% of 112 samples within 20% AC-055-312 100% of 32 samples within 20%	67896062PAH1006 98.9% of 186 samples within 20% 67896062PAH1008: 98.5% of 67 samples within 20% 67896062PAH1010: 100% of 112 samples within 20% AC-055-312 100% of 31 samples within 20%
Selectivity (including hemolyzed and hyperlipidemic plasma)	no relevant interferences	no relevant interferences
Matrix effect	no relevant interferences	no relevant interferences
Stability in blood	2 h at melting ice and room temperature	2 h at melting ice and room temperature
Stability in plasma	5 F/T cycles 45 h at room temperature 1270 d at -20 and 379 d at -70°C	5 F/T cycles 45 h at room temperature 1270 d at -20 and 379 d at -70°C
Processed sample stability	96 h at 10°C	96 h at 10°C
Stability in stock solution	24 h at room temperature 79 d at -70°C	24 h at room temperature 79 d at -70°C

Source: Appendix 3, Module 2.7.1

Table 37. Bioanalytical Method Validation Performance Summary for Method BA-13.225 at Actelion (Used in Study AC-055-121)

BA-13.225 (Actelion) [Mod5.3.1.4/BA-13.225]	Macitentan	Aprocitentan
Matrix	plasma	plasma
Validated concentration range	1-2,000 ng/mL	1-2,000 ng/mL
Inter-run accuracy (%)	97.6-108.7	100.2-107.7
Inter-run precision (%CV)	3.3-11.6	4.0-6.4
Intra-run accuracy (%)	95.8-119.3	98.1-110.2
Intra-run precision (%CV)	2.0-10.2	2.0-8.3
Intra-run accuracy (10/50 [a] x dilution) (%)	96.2/99.8 [a]	98.8/109.3 [a]
Intra-run precision (10/50 [a] x dilution) (%CV)	4.3/1.1 [a]	4.0/1.9 [a]
Incurred sample reproducibility	Study AC-055-121: 89.3% of 56 samples within 20%	Study AC-058-101: 87.5% of 56 samples within 20%
Selectivity (including hemolyzed and hyperlipidemic plasma)	no relevant interferences	no relevant interferences
Matrix effect	no relevant interferences	no relevant interferences
Stability in plasma	5 F/T cycles[a] 208 [a] d at -80°C 1,074 d at -25°C[b] 3 d at room temperature[b]	5 F/T cycles[a] 208 [a] d at -80°C 1,074 d at -25°C[b] 3 d at room temperature[b]
Processed sample stability	69 h at 4°C	69 h at 4°C
Stability in stock solution	16 h at room temperature 23 d at -80°C	16 h at room temperature 53 d at -80°C

[a] Information from BA-14.033.
[b] Amendment 1 of SBA_S_04081.

Source: Appendix 3, Module 2.7.1

For all four studies, study samples, calibration standards, and quality control (QC) samples were analyzed within established period of frozen stability at -20°C. Incurred sample reanalysis (ISR) was performed with adequate number of study samples, and the ISR results were within the

acceptance criteria for both analytes.

It should be noted that Studies 67896062PAH1008, 67896062PAH1010, and AC-055-312 (TOMORROW) were conducted prior to the Agency's implementation of the *M10 Bioanalytical Method Validation and Sample Analysis Guidance* (https://www.fda.gov/media/162903/download) in November 2022 and therefore, the bioanalytical method validation was performed according to the *Guidance to Industry: Bioanalytical Method Validation* (https://www.fda.gov/media/70858/download) that was issued in May 2018. Study AC-055-121 was conducted in 2015 and therefore, the bioanalytical method validation was performed according to the *Guidance to Industry: Bioanalytical Method Validation* that was issued in 2013.

Overall Conclusion for Bioanalytical Methods:

The acceptance criteria and performance of the bioanalytical methods are in compliance with the Agency's *Guidance for Industry: Bioanalytical Method Validation* (https://www.fda.gov/media/70858/download). The method validation and performance of the bioanalytical method used for measurements of macitentan and aprocitentan in sample analysis from Studies AC-055-121, 67896062PAH1008, 67896062PAH1010, and AC-055-312 (TOMORROW) are acceptable.

13.2. Pharmacometrics Assessment

13.2.1 Population PK analysis

13.2.1.1 Review Summary

In general, the Applicant's population PK (PopPK) analysis is considered acceptable for the purpose of characterizing the PK profile of macitentan and its active metabolite aprocitentan in pediatric patients with PAH. The Applicant's analyses were verified by the reviewer, with no significant discordance identified. As noted elsewhere, the Applicant is not seeking an indication for the treatment of pediatric PAH in this supplement. Specific comments on the Applicant's final population PK model are shown in **Table 38**.

Table 38. Specific Comments on Applicant's Final Population PK model

Utility of the final model			Reviewer's Comments
Support applicant's proposed labeling statements about intrinsic and extrinsic factors	**Intrinsic factor**	There is no proposed change related to intrinsic factor and PopPK in the label.	N/A
	Extrinsic factor	N/A	N/A

13.2.1.2 Introduction

The primary objectives of the Applicant's analysis were to:

- Update the previously developed population PK model of macitentan with all the available PK data collected in pediatric participants with PAH enrolled in Study AC-055-312 and Study 67896062PAH3001 (hereafter referred to as PAH3001) (Clinical cutoff date: May 12, 2023).
- Develop a population PK model to describe the PK of aprocitentan in all the pediatric participants with PAH enrolled in Study AC-055-312 and Study PAH3001.
- Determine the individual estimates of macitentan and aprocitentan $AUC_{0\text{-}24h,ss}$, and the combined unbound macitentan and aprocitentan $AUC_{0\text{-}24h,ss}$ obtained by accounting for the in vitro potency and plasma protein binding differences ($AUC_{u,combo,ss}$).
- Compare the pediatric $AUC_{u,combo,ss}$ obtained with the current dose regimen in the different age and body weight groups with the $AUC_{u,combo,ss}$ obtained in adults at a dose of 10 mg.

13.2.1.3 Model development

Data

The final analysis dataset (macitentan_pool_21Jul2023_mod_TSLD2.csv) included 20 adult participants and 57 pediatric participants. Nine subjects were <2 years (N=7 from Study AC-055-312 and N=2 from Study PAH3001). Brief descriptions of the studies are presented in **Table 39**. Detailed samples in each age and weight categories are listed in **Table 40**.

Table 39. Overview of Pediatric and Adult Data Included in the PopPK analysis

Study (NCT number)	Population	Dosing Regimen	PK Sampling
Study AC-055-312 (NCT02932410) N=55	Male and female participants with symptomatic PAH between ≥2 and <18 years of age	Dispersible tablets (CSF or FMI) (pediatric formulation) Oral macitentan at multiple doses of 3.5, 5, 7.5, or 10 mg based on weight, once daily	PK samples at steady state: (predose, 1, 2, 4, 8, 12, 24 h) in a subset of up to 40 participants Trough concentration at Week 12
	Male and female participants with symptomatic PAH between ≥1 month and <2 years of age	Dispersible tablets (CSF or FMI) (pediatric formulation) Oral macitentan at multiple doses of 1 or 2.5 mg based on age, once daily	PK samples at Day 1: (2, 5, and 24 h) Trough concentration at Week 4 and Week 8
PAH3001 (NCT05167825) N=2	Male and female Japanese participants with symptomatic PAH between ≥3 months and <2 years of age	Dispersible tablets (FMI) (pediatric formulation) Oral macitentan at multiple doses of 1 or 2.5 mg based on age, once daily	PK samples at Day 1: (2, 5 and 24 h) Trough concentration at Week 4 and Week 8
AC-055-303_PK (NCT00667823) N=20	Male and female participants with symptomatic PAH	Film-coated tablets (adult formulation) Oral macitentan at multiple doses of 10 mg once daily	PK samples at steady state: (predose, 1, 3, 5, 6, 7, 8, 9, 10, 12, 14, 24 h)

CSF=clinical service formulation; FMI=final market image; N=number of participants; PAH=pulmonary arterial hypertension; PK=pharmacokinetics;

Source: Table 2 in PopPK report, Macitentan Population Pharmacokinetics Model and Exposure Assessment in Pulmonary Arterial Hypertension in Pediatric Patients (Apr. 9, 2024)

Table 40. Summary of Participants and PK Observations Included in the Analysis Dataset, Stratified by Study and Age and Weight Categories

Study	Age and Weight Categories	Number of Participants With Available Observations	Number of Macitentan Observations	Number of Aprocitentan Observations
Total		77	520	520
AC-055-303_PK		20	240	240
AC-055-312	Overall	57	280	280
Participants included in the PK substudy	≥6 months and <2 years	9	37	37
	≥2 years, ≥10 kg and <15 kg	3	24	24
	≥2 years, ≥15 kg and <25 kg	6	48	48
	≥2 years, ≥25 kg and <50 kg	11	80	80
	≥2 years, ≥50 kg	9	72	72
Participants included only in the main study	≥2 years, ≥10 kg and <15 kg	2	2	2
	≥2 years, ≥15 kg and <25 kg	4	4	4
	≥2 years, ≥25 kg and <50 kg	8	8	8
	≥2 years, ≥50 kg	5	5	5

Source: Table 3 in PopPK report, Macitentan Population Pharmacokinetics Model and Exposure Assessment in Pulmonary Arterial Hypertension in Pediatric Patients (Apr. 9, 2024)

The Applicant used different dose according to the pediatric patients' body weight and age in Study #AC-055-312 and #PAH3001 as shown below (**Table 40**).

Table 41. Dosing Regimen by Age and Body Weight in Study AC-055-312 and PAH 3001

Age and Body Weight Categories	Daily Dose (mg)
≥1 month and <6 months	1
≥6 months and <2 years	2.5
≥2 years, ≥10 kg and <15 kg	3.5
≥2 years, ≥15 kg and <25 kg	5
≥2 years, ≥25 kg and <50 kg	7.5
≥2 years, ≥50 kg	10 (consistent with the adult daily dose)

Source: Table 1 in PopPK report, Macitentan Population Pharmacokinetics Model and Exposure Assessment in Pulmonary Arterial Hypertension in Pediatric Patients (Apr. 9, 2024)

Nonlinear mixed effect modeling of concentration-time data was performed using NONMEM (Version 7.3) with first-order conditional estimation approximation. Modifications to the analysis dataset, exploratory analysis, diagnostic graphics, and postprocessing of NONMEM analysis results were carried out using R software (Version 4.2.0). **Table 42** provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 42. Summary of Baseline Demographic Covariates for Analysis

Demographics	6 mo to <2 y (N=9)	10 to <15 kg (N=5)	15 to <25 kg (N=10)	25 to <50 kg (N=19)	>50 kg (N=14)	Adults (N=20)	Total (N=77)
Body weight (kg)							
Mean (SD)	9.39 (2.02)	11.7 (1.12)	20.8 (3.53)	37.3 (7.72)	58.8 (7.73)	79.8 (18.3)	45.2 (27.9)
Median	9.5	11.8	21.1	38	55.4	73.2	45
[range]	[6.10;13.1]	[10.2;13.2]	[15.2;25.1]	[24.7;46.6]	[50.4;75.6]	[63.5;125]	[6.10;125]
Age (years)							
Mean (SD)	1.74 (0.24)	3.2 (0.837)	7.3 (2.54)	10.5 (2.09)	14.6 (2.10)	44.8 (13.6)	18.2 (17.7)
Median	1.83	3	7.5	10	15	43	12
[range]	[1.17;1.92]	[2;4]	[3;10]	[6;14]	[12;17]	[25;72]	[1.17;72]
Sex							
Female	1 (11.1%)	2 (40.0%)	7 (70.0%)	15 (78.9%)	11 (78.6%)	16 (80.0%)	52 (67.5%)
Male	8 (88.9%)	3 (60.0%)	3 (30.0%)	4 (21.1%)	3 (21.4%)	4 (20.0%)	25 (32.5%)
Race							
White	2 (22.2%)	2 (40.0%)	3 (30.0%)	11 (57.9%)	4 (28.6%)	16 (80%)	38 (49.4%)
Black	2 (22.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (2.6%)
Hispanic	0 (0%)	0 (0%)	0 (0%)	2 (10.5%)	5 (35.7%)	4 (20%)	11 (14.3%)
Asian	3 (33.3%)	1 (20.0%)	4 (40.0%)	2 (10.5%)	2 (14.3%)	0 (0%)	12 (15.6%)
Other	2 (22.2%)	2 (40.0%)	3 (30.0%)	4 (21.1%)	3 (21.4%)	0 (0%)	14 (18.2%)

N=number of participants; SD=standard deviation.

Source: Table 7 in PopPK report, Macitentan Population Pharmacokinetics Model and Exposure Assessment in Pulmonary Arterial Hypertension in Pediatric Patients (Apr. 9, 2024)

Base model

The previous macitentan population PK model was built based on pediatric data from study AC-055-312 and adult data from study AC-055-303 which contains 240 macitentan PK samples from 20 adults and 214 macitentan PK sample from 35 pediatric patients 2-18 years old. The model was applied on the macitentan data in the current dataset. However, the exploration of post hoc estimates of CL and V versus body weight showed an underprediction of the PK parameters for body weight <15 kg and an overprediction for body weight >50 kg, suggesting that a power model with fixed coefficients of 0.75 for CL and 1 for V may not be appropriate to provide the best description of the data available. Therefore, the coefficients were re-estimated, providing an improvement in OFV of 49.057 points ($p < 0.001$). Based on this model, exploration of post hoc estimates of CL versus body weight suggested approximately constant CL for body weight ≥25 kg. As a result, the covariate effect for body weight on macitentan CL was defined as a constant value for participants ≥25 kg, whereas for participants <25 kg, the effect of body weight was included using a power model with estimated coefficient and reference weight of 25 kg (see below).

$$CL_{mac} = \begin{cases} CL_{ref,mac} & subjects \geq 2\ years\ and \geq 25\ kg \\ CL_{ref,mac}\left(\frac{WT}{25}\right)^{WTCL_{mac}} & subjects \geq 2\ years\ and < 25\ kg \\ CL_{ref,mac}\left(\frac{WT}{25}\right)^{WTCL_{mac}} \cdot CL_{CYP,scaled} & subjects < 2\ years \end{cases}$$

CLref,mac is the typical value of clearance in participants ≥25 kg and WT CLmac is the estimated allometric coefficient

Source: Equation 6 in PopPK report, Macitentan Population Pharmacokinetics Model and Exposure Assessment in

For participants <2 years of age, the effect of body weight on CL and V was included considering the value of body weight at the Day 1 visit. CL_{mac} was further scaled by age at baseline using age-dependent ontogeny functions, which describe the maturation of the CYP P450 enzymes primarily involved in the elimination of macitentan (see below). Macitentan is primarily metabolized in the liver by CYP P450 enzymes (relative contributions: 58.0% CYP3A4, 26.1% CYP2C9, 8.40% CYP2C8, and 3.4% CYP2C19 of the total hepatic clearance). The Applicant's model assumed that the entire elimination of macitentan was related to hepatic metabolism, although it is known that 4.1% of macitentan elimination is related to biliary excretion. According to this assumption, the metabolizing fractions (Fi) were scaled to cover 100% of the elimination, which is 60.5% CYP3A4, 27.2 % CYP2C9, 8.76 % CYP2C8, and 3.54% CYP2C19.

$$CL_i = \begin{cases} F_{birth} + \dfrac{(Adult_{max} - F_{birth}) \times Age^n}{AGE_{50}{}^n + Age^n} & AGE < Age_{cap} \\ C_0 + C_1 \times e^{C_2 \times (Age - C_3)} & AGE \geq Age_{cap} \end{cases} \qquad i = \begin{cases} 3A4 \\ 2C8 \\ 2C9 \\ 2C19 \end{cases}$$

$$CL_{CYP} = F_{3A4}CL_{3A4} + F_{2C8}CL_{2C8} + F_{2C9}CL_{2C9} + F_{2C19}CL_{2C19}$$

$$CL_{CYP,scaled} = (1 - max)\frac{(CL_{CYP} - min)}{(max - min)} + max$$

$$CL_{mac} = CL_{ref,mac} \times \left(\frac{WT}{70}\right)^{0.75} \times CL_{CYP,scaled}$$

CL_{CYP} represents the combination of ontogeny functions, each weighted by their relative metabolizing fraction, and $CL_{CYP,scaled}$ represents a scaling transformation of CL_{CYP}, so that the maturation of CL_{mac} reaches 100% at 2 years (min and max are, respectively, the value of CL_{CYP} at 0 and 2 years old)

Parameters of the Ontogeny Functions for the Metabolizing Enzymes of Macitentan and Aprocitentan used in PopPK model

Enzyme	F_{birth}	Age_{50}	n	$Adult_{max}$	Age_{cap}	C_0	C_1	C_2	C_3
CYP3A4	0.11	0.64	1.91	1.06	25	1.1	-0.123	-0.05	2.2
CYP2C8	0.41	0.366	0.68	1.053	20	1	0	0	0
CYP2C9	0.17	0.0157	0.53	0.98	5	1	0	0	0
CYP2C19	0.3	0.29	2.44	0.98	5	1	0	0	0

$Adult_{max}$=maximum maturation for a reference adult subject; Age_{50}=age in years at which the ontogeny function reaches 50% of the maturation relative to adult; Age_{cap}=threshold between the sigmoidal and the exponential increase with age of the ontogeny function; C0,C1,C2,C3=weights parameters of the exponential increase with age of the ontogeny function; CYP=cytochrome P450; F_{birth}=value assumed by the ontogeny function at Age=0 years, describing the fraction of enzyme maturation relative to adult at birth; n=exponent parameter determining the sigmoidal increase with age of the ontogeny function.

Source: Equation 2 and Table 5 in PopPK report, Macitentan Population Pharmacokinetics Model and Exposure Assessment in Pulmonary Arterial Hypertension in Pediatric Patients (Apr. 9, 2024)

Per the label, the systemic exposure to the active metabolite is 3-times the exposure to macitentan and is expected to contribute approximately 40% of the total pharmacologic activity. The original popPK model for aprocitentan showed an underprediction of the PK parameters for body weight

<15 kg and an overprediction for body weight >50 kg. After re-estimating the coefficients using the current dataset, the model adequately describes the PK data along the entire body weight range. To account for aprocitentan metabolism by glucuronidation (25.2% of the total elimination), the effect of age on aprocitentan clearance maturation was added considering the ontogeny function of UGT1A1 as described in the equation below. The remaining part of elimination (ie, 1-F_{1A1}) was assumed to be age-independent.

$$CL_{1A1} = \begin{cases} F_{birth} + \dfrac{(Adult_{max} - F_{birth}) \times Age^{n}}{AGE_{50}{}^{n} + Age^{n}} & AGE < Age_{cap} \\ C_0 + C_1 \times e^{C_2 \times (Age - C_3)} & AGE \geq Age_{cap} \end{cases}$$

$$CL_{UGT} = F_{1A1} CL_{1A1}$$

$$CL_{UGT,scaled} = (1 - max) \frac{(CL_{UGT} - min)}{(max - min)} + max + (1 - F_{1A1})$$

$$CL_{apr} = CL_{ref,apr} \times \left(\frac{WT}{70}\right)^{0.75} \times CL_{UGT,scaled}$$

Parameters of the Ontogeny Functions for the Metabolizing Enzymes of Aprocitentan used in PopPK Model

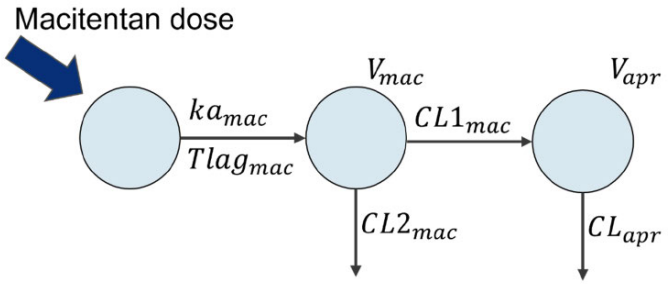
Enzyme	F_{birth}	Age_{50}	n	$Adult_{max}$	Age_{cap}	C_0	C_1	C_2	C_3
UGT1A1	0	0.183	1.105	1	25	1	0	0	0

Adultmax=maximum maturation for a reference adult subject; Age50=age in years at which the ontogeny function reaches 50% of the maturation relative to adult; Agecap=threshold between the sigmoidal and the exponential increase with age of the ontogeny function; C0,C1,C2,C3=weights parameters of the exponential increase with age of the ontogeny function; Fbirth=value assumed by the ontogeny function at Age=0 years, describing the fraction of enzyme maturation relative to adult at birth; n=exponent parameter determining the sigmoidal increase with age of the ontogeny function; UGT=UDP-glucuronosyltransferases.

Source: Equation 3 and Table 6 in PopPK report, Macitentan Population Pharmacokinetics Model and Exposure Assessment in Pulmonary Arterial Hypertension in Pediatric Patients (Apr. 9, 2024)

The final model is a combined model of macitentan and aprocitentan and takes into account the 3 enzymes (CYP3A4, CYP2C8, CYP2C19) involved in the metabolism of macitentan and that contribute to the formation of aprocitentan. The model structure is shown in **Figure 14**. In this model, the formation of aprocitentan and its appearance in plasma depends only on the maturation of macitentan (i.e., the absorption compartment for aprocitentan was removed), and it was assumed equal to 72.8% of the total clearance of macitentan, which corresponds to the sum of the metabolizing fractions of CYP3A4, CYP2C8, and CYP2C19. The combined model gives a drop in OFV and comparable parameter estimates for both macitentan and aprocitentan with two separated models.

Figure 14. Combined PopPK Model Structure



CLapr [L/h]= apparent clearance of aprocitentan; CL_{1mac} and CL_{2mac} [L/h]=72.8% and 28.2% of total macitentan apparent clearance, respectively; ka_{mac} [h^-1]=absorption rate constant for macitentan; $Tlag_{mac}$ [h]=lag time of macitentan absorption; Vapr [L]=apparent volume of distribution for aprocitentan; Vmac [L]=apparent volume of distribution for macitentan.

Source: Figure 3, PopPK report, Macitentan Population Pharmacokinetics Model and Exposure Assessment in Pulmonary Arterial Hypertension in Pediatric Patients (Apr. 9, 2024)

Covariate analysis

Covariate analysis was conducted to explore the relationship between random effects of macitentan and aprocitentan CL and V obtained with the combined model with continuous and categorical covariates such as age, body weight, sex, and race. After the inclusion of body weight on macitentan and aprocitentan CL and V, and of age on macitentan and aprocitentan CL, no trends in these parameter-covariate relationships for age and body weight were observed. In addition, no trends were observed in the parameter-covariate relationships for sex and race and therefore no further covariates were included in the combined model.

13.2.1.4 Final Model

The parameter estimates for the final covariate model are listed in **Table 43**. The model describes the observed data adequately, as seen in the goodness-of fit plots (**Figure 15**). The model over predicts the low concentration range, i.e., below 30 ng/mL for macitentan. In addition, the Applicant indicates in the plot footnote that “Data from pediatric participants <2 years (N=37) were removed for readability”, which is not appropriate; these data points should be included in the plots.

Table 43. Parameter estimates of the final PopPK model

Parameter	Macitentan		Aprocitentan	
	Estimates	RSE%	Estimates	RSE%
ka	0.241	34.1	---	---
Tlag	0.541	44.2	---	---
CL_{ref}	1.49	6.11	0.357	4.96
V_{ref}	39.3	20.2	48.3	27.5
IIV CL (CV%)[a] [shrinkage%]	0.158 (41.4%) [5.96%]	20.1	0.117 (35.2%) [3.18%]	26.0
IIV V (CV%)[a] [shrinkage%]	0.179 (44.3%) [33.9%]	29.7	0.25 (53.3%) [55.2%]	44.4
WT on CL	0.758	20.3	0.568	11.0
WT on V	0.449	16.4	1.19	13.1
RUV (CV%)[a]	0.0858 (29.9%)	24.4	0.0223 (15.0%)	22.8

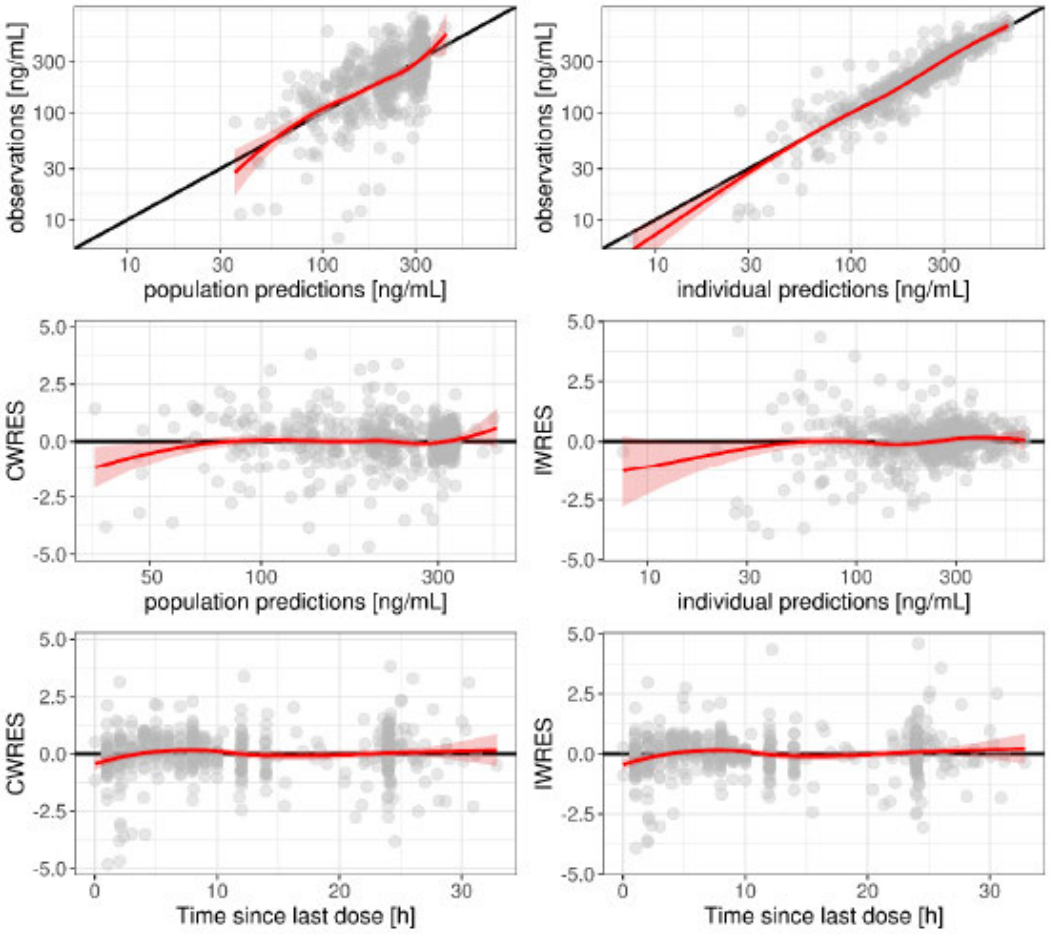
CL=apparent clearance; CLref=apparent clearance for reference weight of 25 kg (macitentan) or 70 kg (aprocitentan); CV=coefficient of variation; IIV=inter individual variability; ka= micro rate constant of absorption / absorption rate constant; PK=pharmacokinetics; RSE=relative standard error; RUV=residual unexplained variability; Tlag=time delay in absorption; V=apparent volume of distribution; Vref=apparent central volume of distribution for reference weight of 70 kg; WT=individual body weight.

[a]CV% are computed using sqrt(exp(ω2)-1)×100.

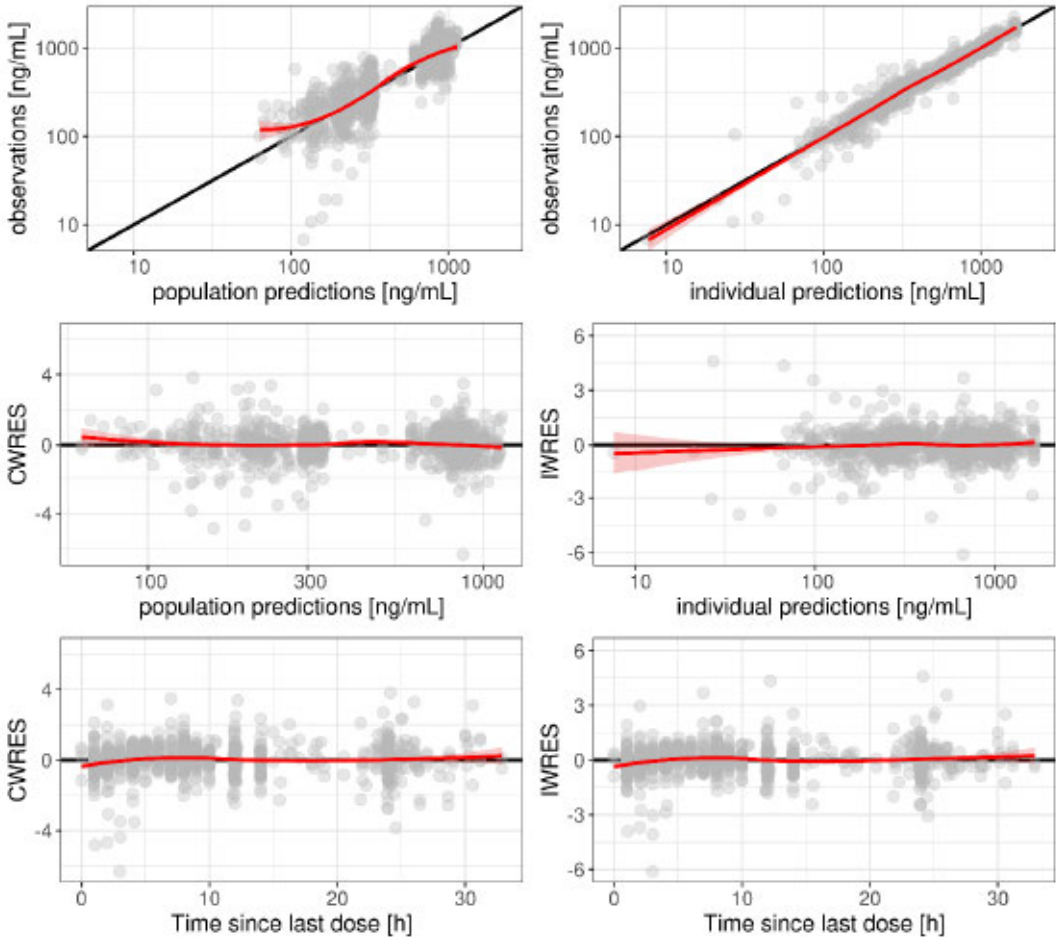
Source: Table 8, PopPK report, Macitentan Population Pharmacokinetics Model and Exposure Assessment in Pulmonary Arterial Hypertension in Pediatric Patients (Apr. 9, 2024)

Figure 15. Goodness-of-Fit Plots for final PopPK Model

Macitentan



Aprocitentan



CWRES=conditional weighted residuals; GOF=goodness-of-fit; IWRES=individual weighted residuals; N=number of participants; PK=pharmacokinetics. Red line: trend of pediatric data.

Red shaded area: 95% confidence interval around the trend of pediatric data. Black horizontal line: reference line.

Data from pediatric participants <2 years (N=37) were removed for readability.

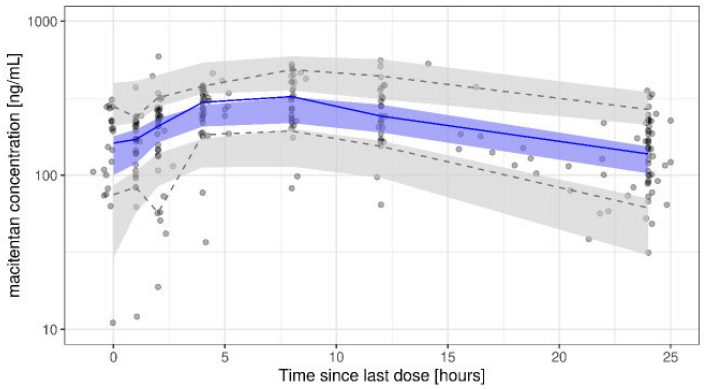
Source: Appendix 9, PopPK report, Macitentan Population Pharmacokinetics Model and Exposure Assessment in Pulmonary Arterial Hypertension in Pediatric Patients (Apr. 9, 2024)

A prediction-corrected visual predictive check (pcVPC) was performed to ensure that the model has maintained fidelity with the observed PK data. Model based simulations of 500 replicates of the analysis data set were performed. Simulated and observed distributions were compared by calculating the median, 5th, and 95th percentiles for each time interval (**Figure 16**). Both final population PK models appeared to capture the central tendency and the variability of the data for both adult and pediatric participants, as attested by the agreement between the observed 10th, 50th, and 90th percentiles of the data and the respective 95% CIs obtained from the simulations.

Figure 16. pcVPC plots for final PopPK Model

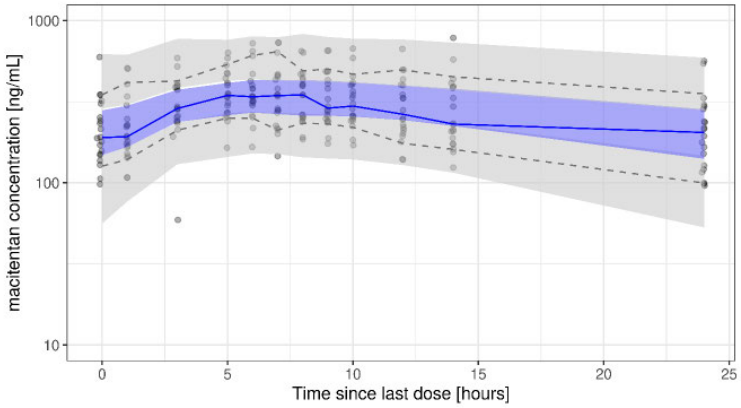
Macitentan

Pediatric patients



Continuous blue line: 50th percentile of macitentan observed data. Dashed gray lines: 10th and 90th percentiles of macitentan observed data. Shaded areas: 95% CI of the corresponding percentiles of the simulated data. Dots: macitentan observed data plotted at the TSLD up to 25 hours. Through data after 25 hours (70 samples) were not displayed for readability. Both observed and simulated data were binned with breaks at times (hours): 0.5, 1.5, 3, 6, 10, 16.

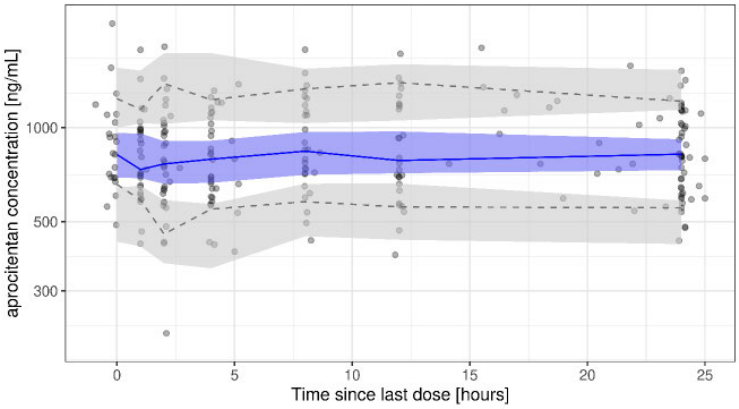
Adults



Continuous blue line: 50th percentile of macitentan observed data. Dashed gray lines: 10th and 90th percentiles of macitentan observed data. Shaded areas: 95% CI of the corresponding percentiles of the simulated data. Dots: macitentan observed data plotted at the TSLD up to 25 hours. Both observed and simulated data were binned with breaks at times (hours): 0.5, 2, 4, 5.5, 6.5, 7.5, 8.5, 9.5, 11, 13, 19.

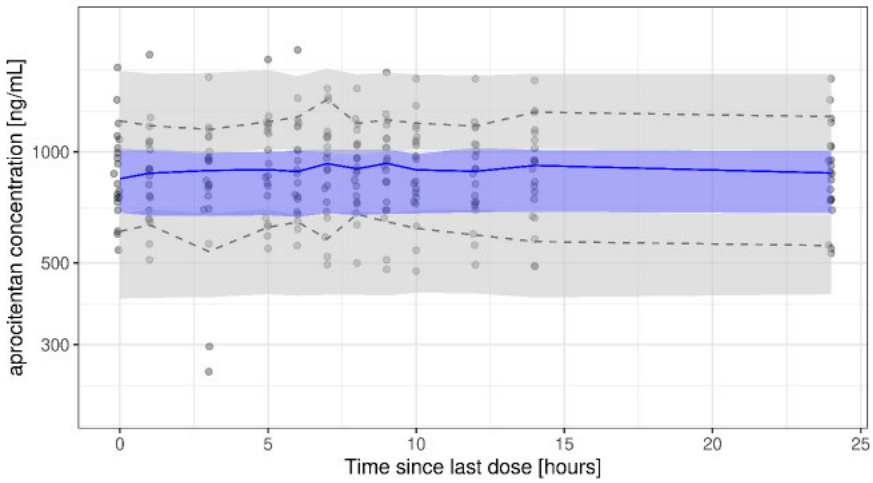
Aprocitentan

Pediatric patients



Continuous blue line: 50th percentile of aprocitentan observed data. Dashed gray lines: 10th and 90th percentiles of aprocitentan observed data. Shaded areas: 95% CI of the corresponding percentiles of the simulated data. Dots: aprocitentan observed data plotted at the TSLD up to 25 hours. Through data after 25 hours (70 samples) were not displayed for readability. Both observed and simulated data were binned with breaks at times (hours): 0.5, 1.5, 3, 6, 10, 16.

Adults



Continuous blue line: 50th percentile of aprocitentan observed data. Dashed gray lines: 10th and 90th percentiles of aprocitentan observed data. Shaded areas: 95% CI of the corresponding percentiles of the simulated data. Dots: aprocitentan observed data plotted at the TSLD up to 25 hours. Both observed and simulated data were binned with breaks at times (hours): 0.5, 2, 4, 5.5, 6.5, 7.5, 8.5, 9.5, 11, 13, 19.

CI=confidence interval; pcVPC=prediction-corrected visual predictive check; PK=pharmacokinetics; TSLD=time since last dose.

Source: Figure 4,5,6 and 7, PopPK report, Macitentan Population Pharmacokinetics Model and Exposure Assessment in Pulmonary Arterial Hypertension in Pediatric Patients (Apr. 9, 2024)

13.2.1.5 PK simulation based on PopPK model

Individual $AUC_{0\text{-}24h,ss}$ of macitentan and aprocitentan were determined for all participants from the post hoc estimates of the final population PK model. Summary statistics of macitentan and aprocitentan $AUC_{0\text{-}24h,ss}$ are reported in **Table 44**.

Table 44. Summary Statistics of Macitentan and Aprocitentan $AUC_{0\text{-}24h,ss}$ from the Final Combined Population PK Model

Macitentan

Population	Stratification	N	Mean	SD	CV%	5%th	Median	95%th	Geometric mean
Adults	---	20	7112	2857	40.2	4050	6398	12516	6629
Pediatrics	overall	57	5204	1800	34.6	2448	5236	8280	4865
	6 mo to 10 to <15 kg	9	3831	1859	48.5	2278	3588	6756	3537
	10 to <15 kg	5	4853	1192	24.6	3819	4127	6249	4740
	15 to <25 kg	10	4734	1285	27.1	3248	4715	6447	4578
	25 to <50 kg	19	5524	1875	33.9	2168	5600	7648	5121
	≥50 kg	14	6112	1680	27.5	3335	6036	8428	5871

Aprocitentan

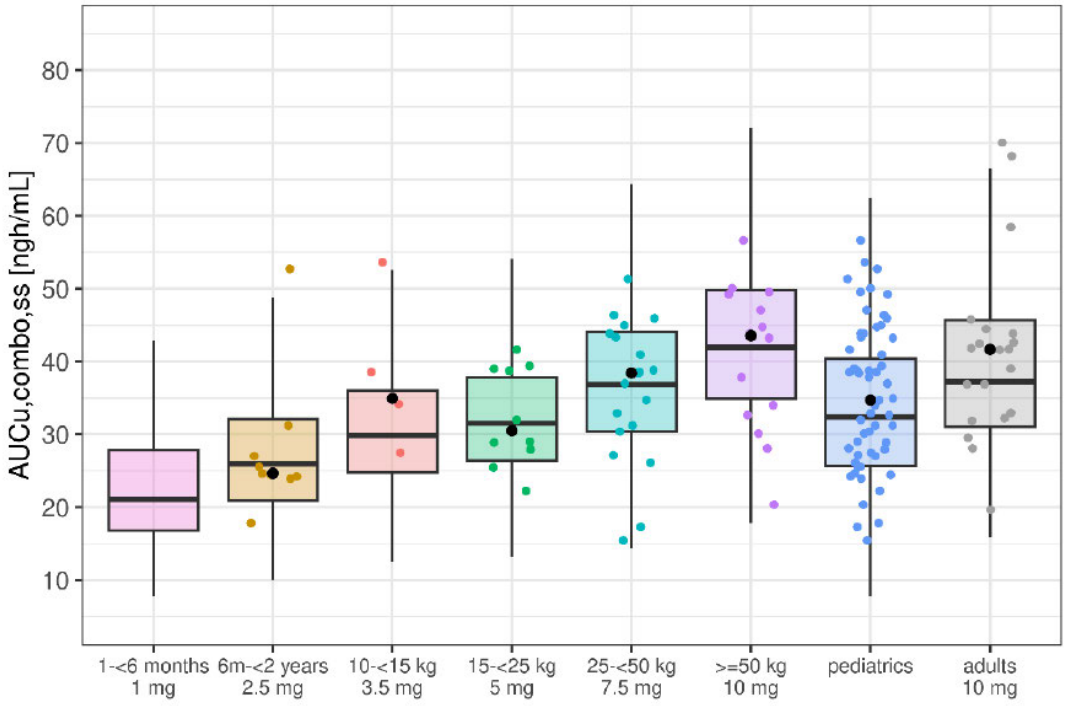
Population	Stratification	N	Mean	SD	CV%	5%th	Median	95%th	Geometric mean
Adults	---	20	21236	6485	30.5	13638	19757	28648	20376
Pediatrics	overall	57	21644	7085	32.7	12660	20826	32406	20384
	6 mo to 10 to <15 kg	9	18224	6935	38.1	8243	19090	26761	16434
	10 to <15 kg	5	25885	9749	37.7	16898	24465	38385	24507
	15 to <25 kg	10	19981	4157	20.8	14561	19534	25570	19587
	25 to <50 kg	19	21149	7362	34.8	12774	18487	31736	19988
	≥50 kg	14	24187	6778	28	14088	25127	33456	23163

$5\%^{th}$, $95\%^{th}$= 5^{th} and 95^{th} percentile; $AUC_{0\text{-}24h,ss}$=area under the plasma concentration-time curve over a 24-hour dosing interval at steady state; CV=coefficient of variation; N=number of participants; PK=pharmacokinetics; SD=standard deviation.

Source: Appendix 15, PopPK report, Macitentan Population Pharmacokinetics Model and Exposure Assessment in Pulmonary Arterial Hypertension in Pediatric Patients (Apr. 9, 2024)

$AUC_{u,combo,ss}$ is also computed by combining unbound exposure parameter computed as the sum of macitentan and aprocitentan $AUC_{0\text{-}24h,ss}$ weighted by their unbound fraction and by their proportion of in vitro potency. Model-based simulations of $AUC_{u,combo,ss}$ are presented in **Figure 17** for different pediatric weight groups (for participants ≥2 years of age) and age groups (for participants <2 years of age), for all pediatric groups combined, and in adults, with the individual estimates of $AUC_{u,combo,ss}$ overlaid. Model simulations showed a comparable distribution of $AUC_{u,combo,ss}$ across pediatric weight groups (for participants ≥2 years of age) and age groups (for participants <2 years of age) and adults, with slightly lower exposures for the 1 - 6 months and 6 - 2 years groups.

Figure 17. Comparison of Simulated and Predicted $AUC_{u,combo,ss}$ Overall and Stratified by Dose Group



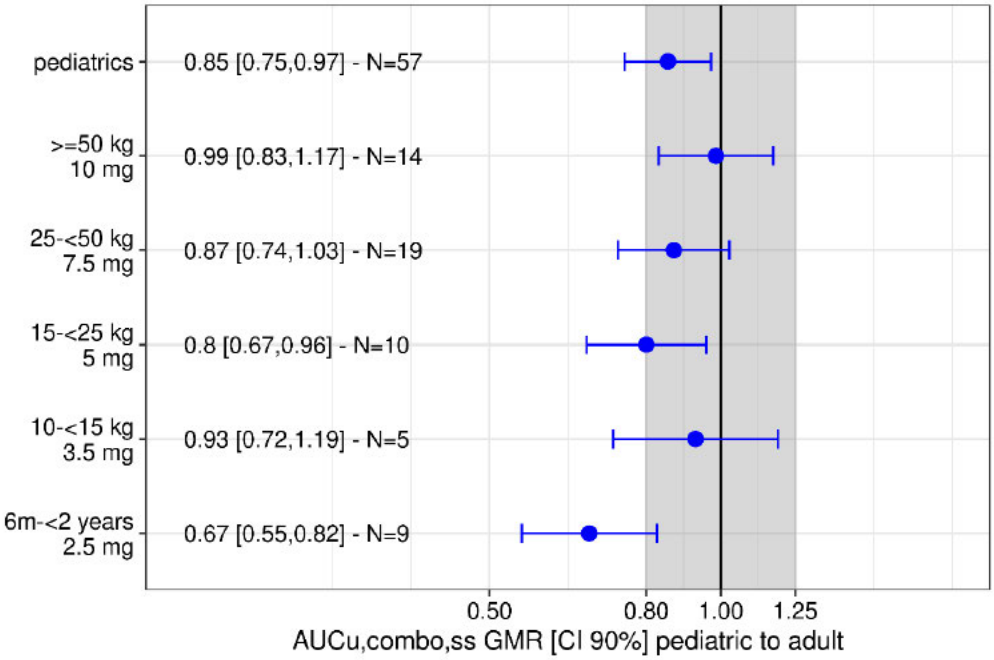
$AUC_{u,combo,ss}$= combined unbound exposure parameter computed as the sum of macitentan and aprocitentan $AUC_{0-24h,ss}$ weighted by their unbound fraction and by their proportion of in vitro potency.

In the plot, "pediatrics" represents all pediatric participants combined and the other 5 groups refer to the different pediatric weight groups (participants ≥2 years of age) and age groups (participants <2 years of age).

Source: Figure 8, PopPK report, Macitentan Population Pharmacokinetics Model and Exposure Assessment in Pulmonary Arterial Hypertension in Pediatric Patients (Apr. 9, 2024)

The GMR and the associated 90% CI of $AUC_{u,combo,ss}$ for each pediatric weight group (participants ≥2 years of age) and age group (participants <2 years of age) versus adults is shown in **Figure 18**. The GMR point estimates were within the 0.8 to 1.25 reference range for all pediatric groups, except the ≥6 months and <2 years group, where the GMR point estimate (0.67) was lower than the reference range. The Applicant attributes the lower exposure to 78% of the participants in the ≥6 months and <2 years group being already older than 20 months at the first day of treatment, and 44% of them reaching 2 years of age during treatment.

Figure 18. Forest Plot of the GMR and 90% CI of Predicted $AUC_{u,combo,ss}$ of Pediatrics (Stratified by Age and Weight Categories) Versus Adult Participants



$AUC_{u,combo,ss}$= combined unbound exposure parameter computed as the sum of macitentan and aprocitentan $AUC_{0-24h,ss}$ weighted by their unbound fraction and by their proportion of in vitro potency; CI=confidence interval; GMR=geometric mean ratio; N=number of participants. In the plot, "pediatrics" represents all pediatric participants combined and the other 5 groups refer to the different pediatric weight groups (participants ≥2 years of age) and age groups (participants <2 years of age).

Source: Figure 9, PopPK report, Macitentan Population Pharmacokinetics Model and Exposure Assessment in Pulmonary Arterial Hypertension in Pediatric Patients (Apr. 9, 2024)

14. TOMORROW Study Design

Table 45. Summary of Baseline Disease Characteristics in Subjects ≥ 2 Years

	Randomized Macitentan	Randomized Standard of Care	Total
Analysis set: FAS1	73	75	148
Pulmonary arterial hypertension etiology			
N	73	75	148
Idiopathic PAH	35 (47.9%)	36 (48.0%)	71 (48.0%)
Heritable PAH	1 (1.4%)	5 (6.7%)	6 (4.1%)
PAH with co-incidental CHD	14 (19.2%)	12 (16.0%)	26 (17.6%)
PAH associated with CHD: post-operative	22 (30.1%)	20 (26.7%)	42 (28.4%)
PAH associated with connective tissue disease	1 (1.4%)	2 (2.7%)	3 (2.0%)
Time from PAH diagnosis to randomization, days			
N	73	75	148
Mean (SD)	698.4 (667.21)	667.2 (791.43)	682.6 (730.48)
Median	491.0	345.0	466.5
Range	(27; 3576)	(29; 4668)	(27; 4668)
IQ range	(131.0; 1157.0)	(100.0; 1031.0)	(105.5; 1076.0)
Right heart catheterization performed to diagnose PAH			
N	73	75	148
Yes	73 (100%)	75 (100%)	148 (100%)
Total number of Signs and symptoms of PAH at baseline reported per subject[1]			
N	57	62	119
Mean (SD)	2.4 (1.68)	2.4 (1.40)	2.4 (1.53)
Median	2.0	2.0	2.0
Range	(1; 9)	(1; 7)	(1; 9)
IQ range	(1.0; 3.0)	(1.0; 3.0)	(1.0; 3.0)
Specification of signs and symptoms of PAH at baseline[1]			
N	57	62	119
Dyspnea with exertion	51 (89.5%)	58 (93.5%)	109 (91.6%)
Dyspnea at rest	4 (7.0%)	3 (4.8%)	7 (5.9%)
Cyanosis with exertion	13 (22.8%)	11 (17.7%)	24 (20.2%)
Cyanosis at rest	5 (8.8%)	8 (12.9%)	13 (10.9%)
Hemoptysis	1 (1.8%)	0	1 (0.8%)
Chest pain/discomfort	7 (12.3%)	12 (19.4%)	19 (16.0%)
Near-syncope/dizziness	8 (14.0%)	2 (3.2%)	10 (8.4%)
Syncope	4 (7.0%)	3 (4.8%)	7 (5.9%)
Fatigue	38 (66.7%)	44 (71.0%)	82 (68.9%)
Hepato-jugular reflux	1 (1.8%)	3 (4.8%)	4 (3.4%)
Hepatomegaly	4 (7.0%)	4 (6.5%)	8 (6.7%)
Peripheral edema	1 (1.8%)	0	1 (0.8%)

	Randomized Macitentan	Randomized Standard of Care	Total
S3 gallop	1 (1.8%)	1 (1.6%)	2 (1.7%)
WHO functional class[2]			
N	73	75	148
I	19 (26.0%)	18 (24.0%)	37 (25.0%)
II	41 (56.2%)	42 (56.0%)	83 (56.1%)
III	13 (17.8%)	15 (20.0%)	28 (18.9%)
Panama functional class			
N	68	72	140
I	16 (23.5%)	19 (26.4%)	35 (25.0%)
II	42 (61.8%)	37 (51.4%)	79 (56.4%)
IIIa	10 (14.7%)	13 (18.1%)	23 (16.4%)
IIIb	0	3 (4.2%)	3 (2.1%)
Ongoing/planned ERA treatment at randomization as per IRT			
N	73	75	148
Yes	33 (45.2%)	34 (45.3%)	67 (45.3%)
No	40 (54.8%)	41 (54.7%)	81 (54.7%)
NT-pro BNP, pmol/L			
N	66	70	136
Mean (SD)	145.33 (414.72)	77.12 (141.14)	110.22 (306.86)
Median	18.23	21.18	20.59
Range	(2.36; 3052.90)	(1.06; 642.04)	(1.06; 3052.90)
IQ range	(7.55; 52.51)	(7.91; 41.42)	(7.85; 51.51)
Baseline BSA-normalized TAPSE[3], mm/m^2			
N	67	69	136
Mean (SD)	14.819 (5.2773)	17.525 (6.8239)	16.192 (6.2382)
Median	13.360	17.610	16.090
Range	(6.44; 29.37)	(5.11; 34.43)	(5.11; 34.43)
IQ range	(10.950; 18.700)	(11.780; 22.570)	(11.220; 20.645)
Baseline left ventricular eccentricity index (diastole)[3]			
N	66	64	130
Mean (SD)	1.462 (0.5036)	1.505 (0.5273)	1.483 (0.5139)
Median	1.380	1.365	1.370
Range	(0.90; 4.20)	(0.90; 4.40)	(0.90; 4.40)
IQ range	(1.100; 1.580)	(1.200; 1.670)	(1.200; 1.600)
Baseline left ventricular eccentricity index (systole)[3]			
N	66	64	130
Mean (SD)	1.815 (0.7144)	1.820 (0.8972)	1.817 (0.8064)
Median	1.535	1.550	1.535
Range	(0.90; 4.30)	(0.80; 5.45)	(0.80; 5.45)
IQ range	(1.300; 2.100)	(1.250; 2.065)	(1.300; 2.100)
Ongoing / Planned SoC at randomization (as per IRT)			
N	73	75	148
Non-PAH-specific therapies	3 (4.1%)	3 (4.0%)	6 (4.1%)

	Randomized Macitentan	Randomized Standard of Care	Total
PDE-5 inhibitor (PDE-5i) monotherapy	39 (53.4%)	36 (48.0%)	75 (50.7%)
ERA monotherapy	7 (9.6%)	5 (6.7%)	12 (8.1%)
PDE-5i + ERA	23 (31.5%)	29 (38.7%)	52 (35.1%)
PDE-5i + inhaled/oral prostanoids	1 (1.4%)	1 (1.3%)	2 (1.4%)
PDE-5i + sGC stimulator	0	1 (1.3%)	1 (0.7%)

Key: BSA = Body surface area; CHD = Congenital heart disease; ERA = Endothelin receptor antagonist; HIV = Human immunodeficiency virus; IQ = Interquartile; IRT = Interactive response technology; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PDE-5i = Phosphodiesterase type 5 inhibitor; SD = Standard deviation; sGC = Soluble guanylate cyclase stimulator; SoC = Standard of care; TAPSE = Tricuspid annular plane systolic excursion; WHO = World Health Organization.

[1] A subject may have more than one sign or symptom denoting PAH reported as present.

[2] Subjects with WHO functional class IV at baseline are not eligible as per inclusion criteria.

[3] As per central review of echocardiogram.

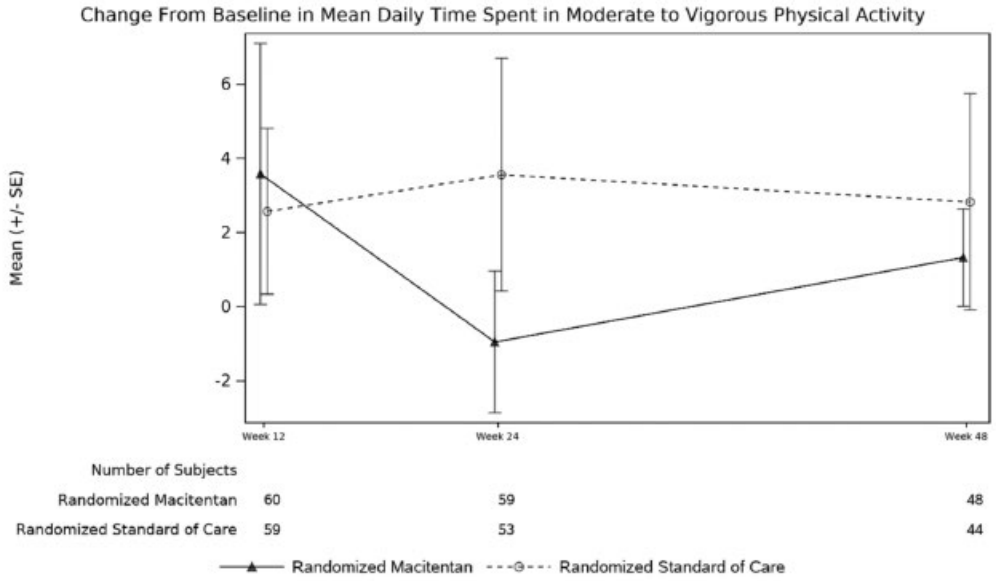
[tsidem04.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_cco5/tsidem04.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-28 ; Production Date: 07MAR2024, 08:35

Source: Table 9, AC-055-312 CSR End of Core Period

15. TOMORROW Efficacy

The Applicant's results for endpoints derived from accelerometry, echocardiography and PedsQL are shown below. As a whole, there were no obvious or consistent effects on these endpoints.

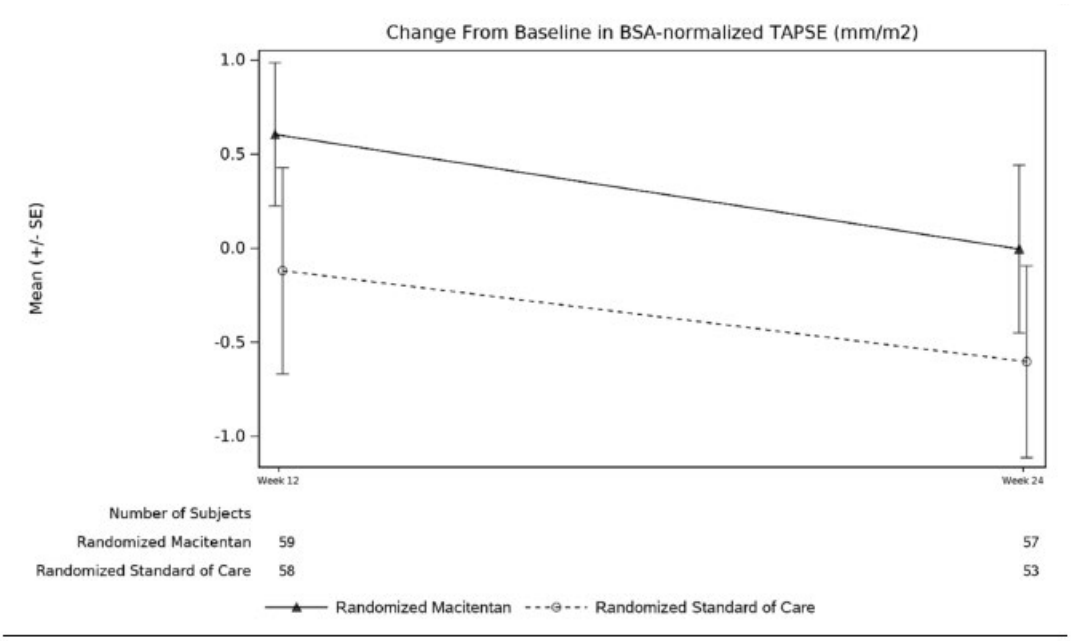
Figure 19. Mean Change from Baseline in Daily Time Spent in Moderate to Vigorous Physical Activity



Key: SE = Standard error.
Note: Threshold for moderate to vigorous physical activity is 3200 activity counts per minute.
[gefpa01ph.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_post_hoc/gefpa01ph.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-28 ; Production Date: 15MAR2024, 05:36

Source: Figure 10, AC-055-312 CSR End of Core Period

Figure 20. Mean Change from Baseline in BSA-Normalized TAPSE

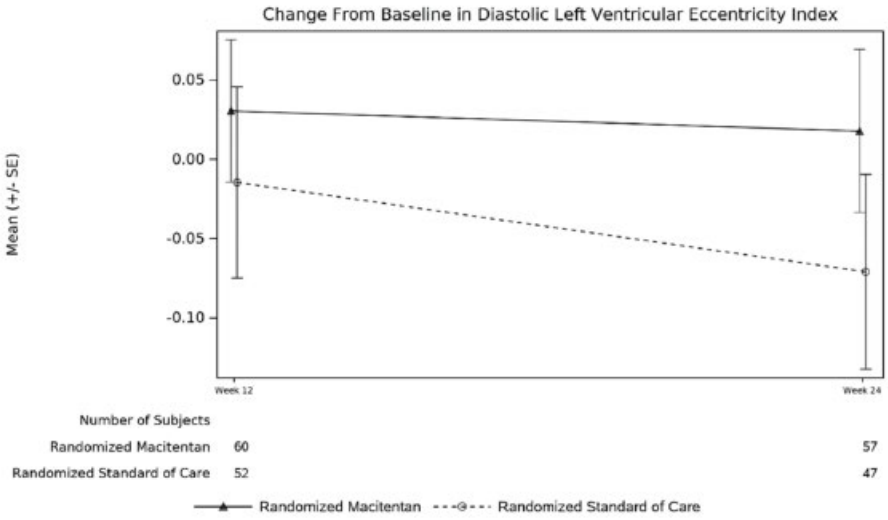


Key: BSA = Body surface area; SE = Standard error; TAPSE = Tricuspid annular plane systolic excursion.

[gefecho01ph.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_post_hoc/gefecho01ph.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-28 ; Production Date: 15MAR2024, 05:36

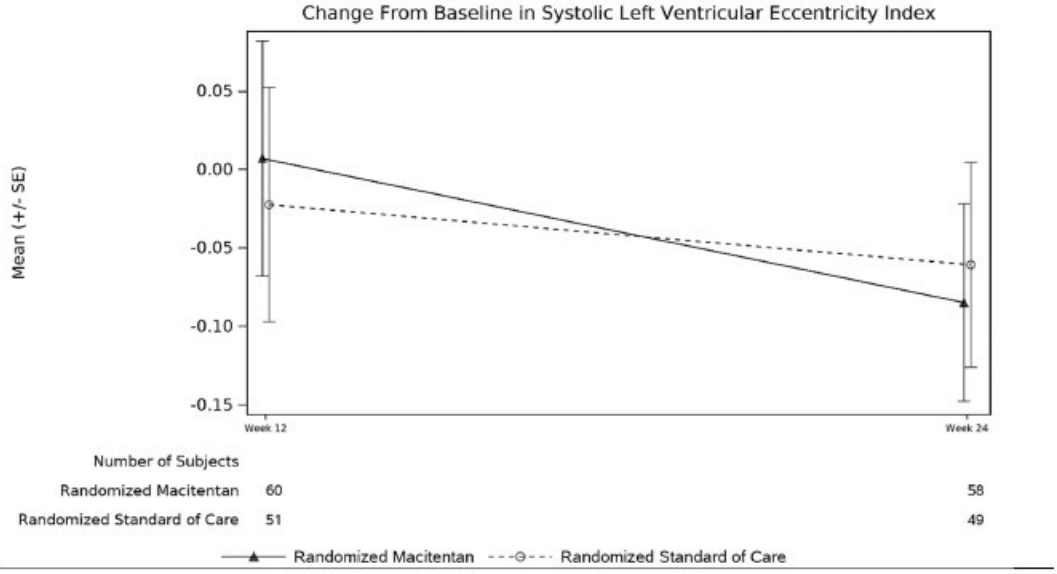
Source: Figure 11, AC-055-312 CSR End of Core Period

Figure 21. Mean Change from Baseline in Diastolic LVEI (top) and Systolic LVEI (bottom)



Key: SE = Standard error.

[gefecho02ph.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_post_hoc/gefecho02ph.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-28 ; Production Date: 15MAR2024, 05:36

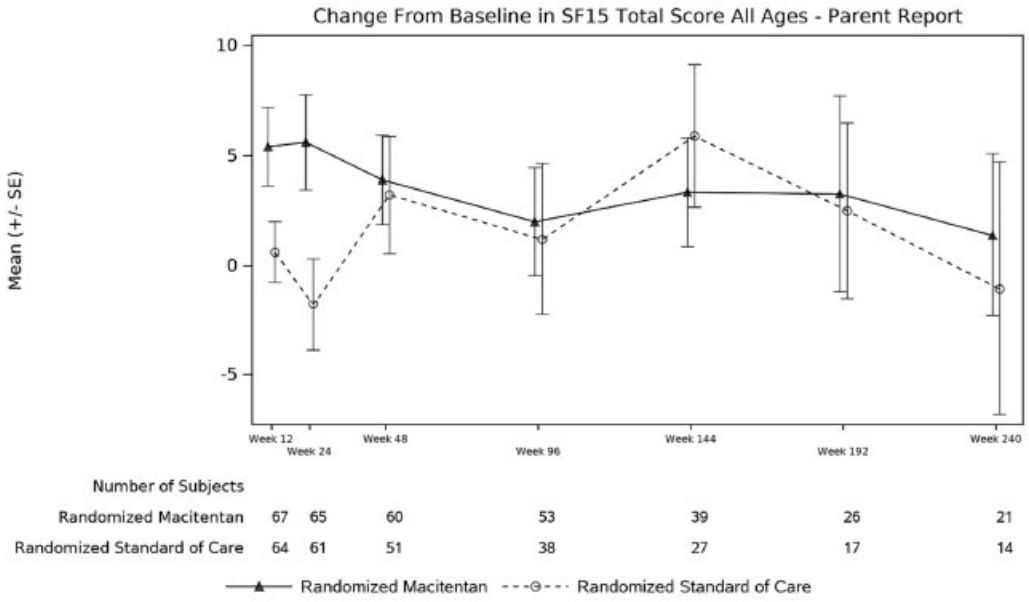


Key: SE = Standard error.

[gefecho03ph.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_post_hoc/gefecho03ph.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-28 ; Production Date: 15MAR2024, 05:36

Source: Figure 12 and 13, AC-055-312 CSR End of Core Period

Figure 22. Mean Change from Baseline in in Short Form (SF15) Generic Core Scales Total Score All Ages - Parent Report Over Time)



Source: Figure 14, AC-055-312 CSR End of Core Period

16. TOMORROW Clinical Safety

Table 46. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

TSFAE02: Number of Subjects With Adverse Events by System Organ Class and Preferred Term – by Period for Subjects ≥ 2 Years Old; SAS1 Analysis Set (Study AC-055-312)

	Main treatment period[1]		Overall core period[2]	
	Randomized Macitentan	Randomized Standard of Care	Randomized Macitentan	Randomized Standard of Care
Analysis set: SAS1	72	75	72	75
Subjects with 1 or more AEs	67 (93.1%)	51 (68.0%)	67 (93.1%)	57 (76.0%)
System organ class Preferred term				
Infections and infestations	58 (80.6%)	38 (50.7%)	59 (81.9%)	43 (57.3%)
Upper respiratory tract infection	23 (31.9%)	12 (16.0%)	23 (31.9%)	13 (17.3%)
Nasopharyngitis	14 (19.4%)	11 (14.7%)	14 (19.4%)	12 (16.0%)
COVID-19	11 (15.3%)	5 (6.7%)	11 (15.3%)	8 (10.7%)
Gastroenteritis	8 (11.1%)	1 (1.3%)	9 (12.5%)	2 (2.7%)
Influenza	8 (11.1%)	3 (4.0%)	8 (11.1%)	4 (5.3%)
Rhinitis	6 (8.3%)	2 (2.7%)	6 (8.3%)	3 (4.0%)
Bronchitis	5 (6.9%)	5 (6.7%)	5 (6.9%)	8 (10.7%)
Pharyngitis	5 (6.9%)	6 (8.0%)	5 (6.9%)	6 (8.0%)
Pneumonia	5 (6.9%)	2 (2.7%)	5 (6.9%)	2 (2.7%)
Respiratory tract infection	4 (5.6%)	3 (4.0%)	4 (5.6%)	3 (4.0%)
Urinary tract infection	4 (5.6%)	3 (4.0%)	4 (5.6%)	3 (4.0%)
Lower respiratory tract infection	3 (4.2%)	1 (1.3%)	3 (4.2%)	1 (1.3%)
Tonsillitis	3 (4.2%)	0	4 (5.6%)	1 (1.3%)
Viral infection	3 (4.2%)	2 (2.7%)	3 (4.2%)	2 (2.7%)
Viral upper respiratory tract infection	3 (4.2%)	2 (2.7%)	3 (4.2%)	3 (4.0%)
Conjunctivitis	2 (2.8%)	2 (2.7%)	2 (2.8%)	2 (2.7%)
Respiratory tract infection viral	2 (2.8%)	1 (1.3%)	2 (2.8%)	1 (1.3%)
Sinusitis	2 (2.8%)	1 (1.3%)	2 (2.8%)	1 (1.3%)
Upper respiratory tract infection bacterial	2 (2.8%)	0	2 (2.8%)	0
Varicella	2 (2.8%)	0	2 (2.8%)	1 (1.3%)
Cellulitis	1 (1.4%)	1 (1.3%)	1 (1.4%)	2 (2.7%)
Cellulitis orbital	1 (1.4%)	0	1 (1.4%)	0
Dengue fever	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Diarrhoea infectious	1 (1.4%)	0	1 (1.4%)	0
Dientamoeba infection	1 (1.4%)	0	1 (1.4%)	0
Ear infection	1 (1.4%)	0	2 (2.8%)	0
Enterovirus infection	1 (1.4%)	0	1 (1.4%)	0
Hand-foot-and-mouth disease	1 (1.4%)	0	1 (1.4%)	0
Infectious mononucleosis	1 (1.4%)	0	1 (1.4%)	0
Laryngitis	1 (1.4%)	2 (2.7%)	1 (1.4%)	3 (4.0%)
Latent tuberculosis	1 (1.4%)	0	1 (1.4%)	0
Localised infection	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Measles	1 (1.4%)	0	1 (1.4%)	0
Mucosal infection	1 (1.4%)	0	1 (1.4%)	0
Oral candidiasis	1 (1.4%)	0	1 (1.4%)	0
Oral herpes	1 (1.4%)	0	1 (1.4%)	0
Otitis media	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Pharyngitis streptococcal	1 (1.4%)	0	1 (1.4%)	0
Pharyngotonsillitis	1 (1.4%)	2 (2.7%)	1 (1.4%)	2 (2.7%)
Pneumocystis jirovecii pneumonia	1 (1.4%)	0	1 (1.4%)	0
Pneumonia mycoplasmal	1 (1.4%)	0	1 (1.4%)	0
Respiratory syncytial virus bronchiolitis	1 (1.4%)	0	1 (1.4%)	0
Respiratory syncytial virus infection	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Salpingo-oophoritis	1 (1.4%)	0	1 (1.4%)	0

	Main treatment period[1]		Overall core period[2]	
	Randomized Macitentan	Randomized Standard of Care	Randomized Macitentan	Randomized Standard of Care
Scarlet fever	1 (1.4%)	0	1 (1.4%)	0
Suspected COVID-19	1 (1.4%)	2 (2.7%)	1 (1.4%)	2 (2.7%)
Wound infection	1 (1.4%)	0	1 (1.4%)	0
Acute sinusitis	0	0	0	1 (1.3%)
Bacterial infection	0	1 (1.3%)	0	1 (1.3%)
Chikungunya virus infection	0	1 (1.3%)	0	1 (1.3%)
Chronic tonsillitis	0	0	0	1 (1.3%)
Coronavirus infection	0	1 (1.3%)	0	1 (1.3%)
Gastroenteritis viral	0	1 (1.3%)	0	1 (1.3%)
Herpes pharyngitis	0	0	0	1 (1.3%)
Mediastinitis	0	1 (1.3%)	0	1 (1.3%)
Otitis externa	0	1 (1.3%)	0	1 (1.3%)
Otitis media acute	0	0	0	1 (1.3%)
Parotitis	0	0	0	1 (1.3%)
Tracheitis	0	1 (1.3%)	0	1 (1.3%)
Tracheobronchitis	0	1 (1.3%)	0	1 (1.3%)
Viral pharyngitis	0	0	0	1 (1.3%)
Viral tracheitis	0	1 (1.3%)	0	1 (1.3%)
Respiratory, thoracic and mediastinal disorders	28 (38.9%)	22 (29.3%)	28 (38.9%)	25 (33.3%)
Cough	6 (8.3%)	3 (4.0%)	7 (9.7%)	5 (6.7%)
Nasal congestion	6 (8.3%)	1 (1.3%)	7 (9.7%)	1 (1.3%)
Oropharyngeal pain	6 (8.3%)	4 (5.3%)	6 (8.3%)	4 (5.3%)
Epistaxis	5 (6.9%)	8 (10.7%)	5 (6.9%)	9 (12.0%)
Rhinitis allergic	4 (5.6%)	2 (2.7%)	4 (5.6%)	2 (2.7%)
Dyspnoea	2 (2.8%)	0	2 (2.8%)	1 (1.3%)
Rhinorrhoea	2 (2.8%)	2 (2.7%)	2 (2.8%)	2 (2.7%)
Wheezing	2 (2.8%)	0	2 (2.8%)	0
Asthma	1 (1.4%)	3 (4.0%)	1 (1.4%)	3 (4.0%)
Asthmatic crisis	1 (1.4%)	0	1 (1.4%)	0
Bronchial obstruction	1 (1.4%)	0	1 (1.4%)	0
Bronchospasm	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Dysphonia	1 (1.4%)	0	1 (1.4%)	0
Haemoptysis	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Laryngeal stenosis	1 (1.4%)	0	1 (1.4%)	0
Pleural effusion	1 (1.4%)	0	1 (1.4%)	0
Productive cough	1 (1.4%)	2 (2.7%)	1 (1.4%)	2 (2.7%)
Pulmonary oedema	1 (1.4%)	0	1 (1.4%)	0
Acute respiratory failure	0	1 (1.3%)	0	1 (1.3%)
Adenoidal hypertrophy	0	0	0	1 (1.3%)
Haemothorax	0	1 (1.3%)	0	1 (1.3%)
Hypoxia	0	1 (1.3%)	0	1 (1.3%)
Pulmonary arterial hypertension	0	0	0	1 (1.3%)
Pulmonary embolism	0	1 (1.3%)	0	1 (1.3%)
Respiratory failure	0	0	1 (1.4%)	0
Sneezing	0	0	0	1 (1.3%)
Systemic sclerosis pulmonary	0	1 (1.3%)	0	1 (1.3%)
Tonsillar hypertrophy	0	1 (1.3%)	0	2 (2.7%)
Upper respiratory tract inflammation	0	0	0	1 (1.3%)
Gastrointestinal disorders	25 (34.7%)	16 (21.3%)	25 (34.7%)	16 (21.3%)
Diarrhoea	7 (9.7%)	6 (8.0%)	7 (9.7%)	6 (8.0%)

	Main treatment period[1]		Overall core period[2]	
	Randomized Macitentan	Randomized Standard of Care	Randomized Macitentan	Randomized Standard of Care
Abdominal pain	5 (6.9%)	6 (8.0%)	5 (6.9%)	6 (8.0%)
Vomiting	5 (6.9%)	8 (10.7%)	5 (6.9%)	8 (10.7%)
Nausea	3 (4.2%)	3 (4.0%)	3 (4.2%)	3 (4.0%)
Dental caries	2 (2.8%)	0	2 (2.8%)	0
Gastritis	2 (2.8%)	1 (1.3%)	2 (2.8%)	1 (1.3%)
Gastrooesophageal reflux disease	2 (2.8%)	0	2 (2.8%)	0
Odynophagia	2 (2.8%)	1 (1.3%)	2 (2.8%)	1 (1.3%)
Toothache	2 (2.8%)	1 (1.3%)	2 (2.8%)	1 (1.3%)
Abdominal pain upper	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Breath odour	1 (1.4%)	0	1 (1.4%)	0
Constipation	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Dyspepsia	1 (1.4%)	0	1 (1.4%)	0
Gingival hypertrophy	1 (1.4%)	0	1 (1.4%)	0
Haematochezia	1 (1.4%)	0	1 (1.4%)	0
Lip ulceration	1 (1.4%)	0	1 (1.4%)	0
Loose tooth	1 (1.4%)	0	1 (1.4%)	0
Oral pain	1 (1.4%)	0	1 (1.4%)	0
Stomatitis	1 (1.4%)	0	1 (1.4%)	0
Tooth impacted	1 (1.4%)	0	1 (1.4%)	0
Faeces discoloured	0	1 (1.3%)	0	1 (1.3%)
Nervous system disorders	21 (29.2%)	15 (20.0%)	21 (29.2%)	18 (24.0%)
Headache	14 (19.4%)	9 (12.0%)	14 (19.4%)	9 (12.0%)
Dizziness	6 (8.3%)	1 (1.3%)	6 (8.3%)	3 (4.0%)
Coordination abnormal	1 (1.4%)	0	1 (1.4%)	0
Epilepsy	1 (1.4%)	0	1 (1.4%)	0
Hypoaesthesia	1 (1.4%)	0	1 (1.4%)	0
Intellectual disability	1 (1.4%)	0	1 (1.4%)	0
Loss of consciousness	1 (1.4%)	0	1 (1.4%)	0
Migraine	1 (1.4%)	1 (1.3%)	1 (1.4%)	2 (2.7%)
Paraesthesia	1 (1.4%)	0	1 (1.4%)	0
Presyncope	1 (1.4%)	2 (2.7%)	1 (1.4%)	3 (4.0%)
Status epilepticus	1 (1.4%)	0	1 (1.4%)	0
Autonomic nervous system imbalance	0	1 (1.3%)	0	1 (1.3%)
Brain oedema	0	0	0	1 (1.3%)
Hypoxic-ischaemic encephalopathy	0	1 (1.3%)	0	1 (1.3%)
Lethargy	0	1 (1.3%)	0	1 (1.3%)
Syncope	0	0	1 (1.4%)	0
General disorders and administration site conditions	18 (25.0%)	8 (10.7%)	18 (25.0%)	10 (13.3%)
Pyrexia	7 (9.7%)	2 (2.7%)	7 (9.7%)	3 (4.0%)
Fatigue	5 (6.9%)	0	5 (6.9%)	0
Non-cardiac chest pain	5 (6.9%)	3 (4.0%)	5 (6.9%)	4 (5.3%)
Asthenia	2 (2.8%)	0	2 (2.8%)	0
Catheter site irritation	1 (1.4%)	0	1 (1.4%)	0
Chest pain	1 (1.4%)	1 (1.3%)	1 (1.4%)	2 (2.7%)
Discomfort	1 (1.4%)	0	1 (1.4%)	0
Oedema peripheral	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Axillary pain	0	1 (1.3%)	0	1 (1.3%)
Chills	0	1 (1.3%)	0	1 (1.3%)
Feeling abnormal	0	0	0	1 (1.3%)
Influenza like illness	0	1 (1.3%)	0	1 (1.3%)

	Main treatment period[a]		Overall core period[b]	
	Randomized Macitentan	Randomized Standard of Care	Randomized Macitentan	Randomized Standard of Care
Infusion site pain	0	1 (1.3%)	0	1 (1.3%)
Injury, poisoning and procedural complications	16 (22.2%)	8 (10.7%)	16 (22.2%)	10 (13.3%)
Arthropod bite	3 (4.2%)	0	3 (4.2%)	0
Fall	2 (2.8%)	1 (1.3%)	2 (2.8%)	1 (1.3%)
Limb injury	2 (2.8%)	0	2 (2.8%)	1 (1.3%)
Animal bite	1 (1.4%)	0	1 (1.4%)	0
Animal scratch	1 (1.4%)	0	1 (1.4%)	0
Concussion	1 (1.4%)	0	1 (1.4%)	0
Contusion	1 (1.4%)	0	1 (1.4%)	0
Face injury	1 (1.4%)	0	1 (1.4%)	0
Foot fracture	1 (1.4%)	0	1 (1.4%)	0
Hand fracture	1 (1.4%)	0	1 (1.4%)	0
Head injury	1 (1.4%)	0	1 (1.4%)	0
Immunisation reaction	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Muscle strain	1 (1.4%)	0	1 (1.4%)	0
Overdose	1 (1.4%)	0	1 (1.4%)	0
Skin laceration	1 (1.4%)	0	1 (1.4%)	1 (1.3%)
Soft tissue injury	1 (1.4%)	0	1 (1.4%)	0
Thermal burn	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Tibia fracture	1 (1.4%)	0	1 (1.4%)	0
Joint dislocation	0	1 (1.3%)	0	1 (1.3%)
Ligament sprain	0	1 (1.3%)	0	1 (1.3%)
Muscle contusion	0	1 (1.3%)	0	1 (1.3%)
Patella fracture	0	1 (1.3%)	0	1 (1.3%)
Procedural pain	0	1 (1.3%)	0	1 (1.3%)
Skin abrasion	0	1 (1.3%)	0	2 (2.7%)
Investigations	14 (19.4%)	8 (10.7%)	14 (19.4%)	8 (10.7%)
Haemoglobin decreased	4 (5.6%)	0	4 (5.6%)	0
Alanine aminotransferase increased	2 (2.8%)	3 (4.0%)	2 (2.8%)	3 (4.0%)
Weight increased	2 (2.8%)	0	2 (2.8%)	0
Aspartate aminotransferase increased	1 (1.4%)	0	1 (1.4%)	0
Blood creatine phosphokinase increased	1 (1.4%)	0	1 (1.4%)	0
Body temperature increased	1 (1.4%)	0	1 (1.4%)	0
Haemodynamic test	1 (1.4%)	0	1 (1.4%)	0
Heart rate increased	1 (1.4%)	0	1 (1.4%)	0
Oxygen saturation decreased	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Platelet count decreased	1 (1.4%)	0	1 (1.4%)	0
Pulmonary arterial pressure increased	1 (1.4%)	0	1 (1.4%)	0
Transaminases increased	1 (1.4%)	0	1 (1.4%)	0
Anticoagulation drug level increased	0	1 (1.3%)	0	1 (1.3%)
Blood ketone body increased	0	1 (1.3%)	0	1 (1.3%)
Heart rate decreased	0	1 (1.3%)	0	1 (1.3%)
SARS-CoV-2 test positive	0	1 (1.3%)	0	1 (1.3%)
Weight decreased	0	1 (1.3%)	0	1 (1.3%)
Blood and lymphatic system disorders	13 (18.1%)	3 (4.0%)	14 (19.4%)	6 (8.0%)
Anaemia	7 (9.7%)	1 (1.3%)	8 (11.1%)	4 (5.3%)
Antiphospholipid syndrome	1 (1.4%)	0	1 (1.4%)	0
Eosinophilia	1 (1.4%)	0	1 (1.4%)	0
Hypercoagulation	1 (1.4%)	0	1 (1.4%)	0

	Main treatment period[1]		Overall core period[2]	
	Randomized Macitentan	Randomized Standard of Care	Randomized Macitentan	Randomized Standard of Care
Iron deficiency anaemia	1 (1.4%)	1 (1.3%)	1 (1.4%)	2 (2.7%)
Neutropenia	1 (1.4%)	0	1 (1.4%)	0
Polycythaemia	1 (1.4%)	0	1 (1.4%)	0
Thrombocytopenia	1 (1.4%)	0	1 (1.4%)	1 (1.3%)
Mesenteric lymphadenitis	0	1 (1.3%)	0	1 (1.3%)
Reproductive system and breast disorders	11 (15.3%)	2 (2.7%)	11 (15.3%)	4 (5.3%)
Heavy menstrual bleeding	4 (5.6%)	1 (1.3%)	4 (5.6%)	1 (1.3%)
Dysmenorrhoea	3 (4.2%)	0	3 (4.2%)	0
Intermenstrual bleeding	1 (1.4%)	0	1 (1.4%)	0
Penile swelling	1 (1.4%)	0	1 (1.4%)	0
Priapism	1 (1.4%)	0	1 (1.4%)	0
Uterine haemorrhage	1 (1.4%)	0	1 (1.4%)	0
Amenorrhoea	0	0	0	1 (1.3%)
Gynaecomastia	0	1 (1.3%)	0	1 (1.3%)
Polymenorrhoea	0	0	0	1 (1.3%)
Cardiac disorders	9 (12.5%)	4 (5.3%)	9 (12.5%)	4 (5.3%)
Angina pectoris	2 (2.8%)	0	2 (2.8%)	0
Atrial tachycardia	1 (1.4%)	0	1 (1.4%)	0
Cardiac arrest	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Cardiogenic shock	1 (1.4%)	0	1 (1.4%)	0
Palpitations	1 (1.4%)	0	1 (1.4%)	0
Pericardial effusion	1 (1.4%)	0	1 (1.4%)	0
Right ventricular failure	1 (1.4%)	0	1 (1.4%)	0
Sinus tachycardia	1 (1.4%)	0	1 (1.4%)	0
Supraventricular tachycardia	1 (1.4%)	0	1 (1.4%)	0
Tachycardia	1 (1.4%)	0	1 (1.4%)	0
Bradycardia	0	1 (1.3%)	0	1 (1.3%)
Cardiac failure	0	1 (1.3%)	0	1 (1.3%)
Dressler's syndrome	0	1 (1.3%)	0	1 (1.3%)
Pericarditis	0	1 (1.3%)	0	1 (1.3%)
Musculoskeletal and connective tissue disorders	9 (12.5%)	7 (9.3%)	10 (13.9%)	8 (10.7%)
Arthralgia	3 (4.2%)	3 (4.0%)	3 (4.2%)	3 (4.0%)
Costochondritis	1 (1.4%)	0	1 (1.4%)	0
Muscular weakness	1 (1.4%)	0	1 (1.4%)	0
Myalgia	1 (1.4%)	0	2 (2.8%)	0
Osteochondritis	1 (1.4%)	0	1 (1.4%)	0
Pain in extremity	1 (1.4%)	0	1 (1.4%)	0
Scoliosis	1 (1.4%)	0	1 (1.4%)	0
Systemic lupus erythematosus	1 (1.4%)	0	1 (1.4%)	0
Bone pain	0	1 (1.3%)	0	1 (1.3%)
Camptodactyly acquired	0	1 (1.3%)	0	1 (1.3%)
Chest wall haematoma	0	1 (1.3%)	0	1 (1.3%)
Coccydynia	0	1 (1.3%)	0	1 (1.3%)
Groin pain	0	1 (1.3%)	0	1 (1.3%)
Musculoskeletal chest pain	0	2 (2.7%)	0	3 (4.0%)
Neck pain	0	1 (1.3%)	0	1 (1.3%)
Pain in jaw	0	1 (1.3%)	0	1 (1.3%)
Systemic scleroderma	0	0	0	1 (1.3%)

	Main treatment period[1]		Overall core period[2]	
	Randomized Macitentan	Randomized Standard of Care	Randomized Macitentan	Randomized Standard of Care
Skin and subcutaneous tissue disorders	6 (8.3%)	7 (9.3%)	6 (8.3%)	7 (9.3%)
Alopecia	1 (1.4%)	0	1 (1.4%)	0
Dermatomyositis	1 (1.4%)	0	1 (1.4%)	0
Eczema	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Papule	1 (1.4%)	0	1 (1.4%)	0
Seborrhoeic dermatitis	1 (1.4%)	0	1 (1.4%)	0
Urticaria	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Vascular skin disorder	1 (1.4%)	0	1 (1.4%)	0
Acne	0	2 (2.7%)	0	2 (2.7%)
Petechiae	0	1 (1.3%)	0	1 (1.3%)
Rash	0	0	0	1 (1.3%)
Rash erythematous	0	2 (2.7%)	0	2 (2.7%)
Skin hyperpigmentation	0	1 (1.3%)	0	1 (1.3%)
Psychiatric disorders	5 (6.9%)	1 (1.3%)	5 (6.9%)	1 (1.3%)
Depression	2 (2.8%)	0	2 (2.8%)	0
Insomnia	2 (2.8%)	0	2 (2.8%)	0
Speech sound disorder	1 (1.4%)	0	1 (1.4%)	0
Gaming disorder	0	1 (1.3%)	0	1 (1.3%)
Renal and urinary disorders	5 (6.9%)	1 (1.3%)	5 (6.9%)	2 (2.7%)
Acute kidney injury	1 (1.4%)	0	1 (1.4%)	0
Neurogenic bladder	1 (1.4%)	0	1 (1.4%)	0
Pollakiuria	1 (1.4%)	0	1 (1.4%)	0
Urethral cyst	1 (1.4%)	0	1 (1.4%)	0
Urethral stenosis	1 (1.4%)	0	1 (1.4%)	0
Vesicoureteric reflux	1 (1.4%)	0	1 (1.4%)	0
Bladder diverticulum	0	0	0	1 (1.3%)
Glomerulonephritis	0	1 (1.3%)	0	1 (1.3%)
Nephropathy	0	1 (1.3%)	0	1 (1.3%)
Nephrotic syndrome	0	1 (1.3%)	0	1 (1.3%)
Vascular disorders	5 (6.9%)	7 (9.3%)	5 (6.9%)	8 (10.7%)
Hypotension	2 (2.8%)	1 (1.3%)	2 (2.8%)	1 (1.3%)
Aortic stenosis	1 (1.4%)	0	1 (1.4%)	0
Flushing	1 (1.4%)	2 (2.7%)	1 (1.4%)	2 (2.7%)
Orthostatic hypotension	1 (1.4%)	0	1 (1.4%)	0
Cyanosis	0	1 (1.3%)	0	1 (1.3%)
Extremity necrosis	0	1 (1.3%)	0	1 (1.3%)
Haematoma	0	0	0	1 (1.3%)
Hypertension	0	1 (1.3%)	0	1 (1.3%)
Thrombosis	0	1 (1.3%)	0	1 (1.3%)
Metabolism and nutrition disorders	4 (5.6%)	1 (1.3%)	5 (6.9%)	2 (2.7%)
Vitamin D deficiency	2 (2.8%)	1 (1.3%)	2 (2.8%)	1 (1.3%)
Dehydration	1 (1.4%)	0	1 (1.4%)	0
Iron deficiency	1 (1.4%)	0	2 (2.8%)	1 (1.3%)
Decreased appetite	0	1 (1.3%)	0	1 (1.3%)

	Main treatment period[1]		Overall core period[2]	
	Randomized Macitentan	Randomized Standard of Care	Randomized Macitentan	Randomized Standard of Care
Eye disorders	3 (4.2%)	1 (1.3%)	3 (4.2%)	1 (1.3%)
Cataract	1 (1.4%)	0	1 (1.4%)	0
Conjunctivitis allergic	1 (1.4%)	0	1 (1.4%)	0
Vision blurred	1 (1.4%)	0	1 (1.4%)	0
Eye swelling	0	1 (1.3%)	0	1 (1.3%)
Ocular hyperaemia	0	1 (1.3%)	0	1 (1.3%)
Ear and labyrinth disorders	2 (2.8%)	1 (1.3%)	2 (2.8%)	1 (1.3%)
Ear pain	1 (1.4%)	0	1 (1.4%)	0
Vertigo positional	1 (1.4%)	0	1 (1.4%)	0
Vertigo	0	1 (1.3%)	0	1 (1.3%)
Congenital, familial and genetic disorders	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Hypospadias	1 (1.4%)	0	1 (1.4%)	0
Atrial septal defect	0	1 (1.3%)	0	1 (1.3%)
Immune system disorders	1 (1.4%)	3 (4.0%)	1 (1.4%)	3 (4.0%)
Seasonal allergy	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Allergy to vaccine	0	1 (1.3%)	0	1 (1.3%)
Drug hypersensitivity	0	1 (1.3%)	0	1 (1.3%)
Social circumstances	1 (1.4%)	0	2 (2.8%)	0
Diet noncompliance	1 (1.4%)	0	1 (1.4%)	0
Physical disability	0	0	1 (1.4%)	0
Surgical and medical procedures	1 (1.4%)	0	1 (1.4%)	0
Hospitalisation	1 (1.4%)	0	1 (1.4%)	0
Endocrine disorders	0	0	1 (1.4%)	0
Hypothyroidism	0	0	1 (1.4%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	1 (1.3%)
Lipoma	0	0	0	1 (1.3%)

Key: AE = Adverse event; EOCP = End of core period; SoC = Standard of care.
[1] Main treatment period: from randomization up to end of randomized macitentan or SoC + 30 days (or EOCP, whichever comes first), or for crossover subjects up to start of macitentan or end of SoC + 30 days, whichever comes first.
[2] Overall core period: from randomization up to EOCP.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 26.1.
Only AEs with onset date occurring during the period under consideration are included.
[tsfae02.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_cco5/tsfae02.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-28 ; Production Date: 07MAR2024, 08:35

Source: Table 43 AC-055-312 CSR End of Core Period

Table 47. List of Serious Adverse Events Leading to Discontinuation of Study Drug

	Main treatment period[1]		Overall core period[2]	
	Randomized Macitentan	Randomized Standard of Care	Randomized Macitentan	Randomized Standard of Care
Analysis set: SAS1	72	75	72	75
Subjects with 1 or more SAEs	26 (36.1%)	16 (21.3%)	26 (36.1%)	21 (28.0%)
System organ class Preferred term				
Infections and infestations	11 (15.3%)	7 (9.3%)	11 (15.3%)	11 (14.7%)
Pneumonia	5 (6.9%)	1 (1.3%)	5 (6.9%)	1 (1.3%)
Cellulitis	1 (1.4%)	0	1 (1.4%)	0
Dengue fever	1 (1.4%)	0	1 (1.4%)	0
Gastroenteritis	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Lower respiratory tract infection	1 (1.4%)	0	1 (1.4%)	0
Pneumonia mycoplasmal	1 (1.4%)	0	1 (1.4%)	0
Respiratory syncytial virus bronchiolitis	1 (1.4%)	0	1 (1.4%)	0
Respiratory tract infection	1 (1.4%)	2 (2.7%)	1 (1.4%)	2 (2.7%)
Respiratory tract infection viral	1 (1.4%)	0	1 (1.4%)	0
Salpingo-oophoritis	1 (1.4%)	0	1 (1.4%)	0
Upper respiratory tract infection	1 (1.4%)	0	1 (1.4%)	0
Urinary tract infection	1 (1.4%)	0	1 (1.4%)	0
Viral infection	1 (1.4%)	0	1 (1.4%)	0
Wound infection	1 (1.4%)	0	1 (1.4%)	0
COVID-19	0	0	0	2 (2.7%)
Gastroenteritis viral	0	1 (1.3%)	0	1 (1.3%)
Influenza	0	1 (1.3%)	0	1 (1.3%)
Laryngitis	0	1 (1.3%)	0	2 (2.7%)
Mediastinitis	0	1 (1.3%)	0	1 (1.3%)
Tonsillitis	0	0	0	1 (1.3%)
Cardiac disorders	4 (5.6%)	2 (2.7%)	4 (5.6%)	2 (2.7%)
Cardiac arrest	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Cardiogenic shock	1 (1.4%)	0	1 (1.4%)	0
Right ventricular failure	1 (1.4%)	0	1 (1.4%)	0
Sinus tachycardia	1 (1.4%)	0	1 (1.4%)	0
Supraventricular tachycardia	1 (1.4%)	0	1 (1.4%)	0
Pericarditis	0	1 (1.3%)	0	1 (1.3%)
Respiratory, thoracic and mediastinal disorders	4 (5.6%)	3 (4.0%)	4 (5.6%)	4 (5.3%)
Asthma	1 (1.4%)	0	1 (1.4%)	0
Asthmatic crisis	1 (1.4%)	0	1 (1.4%)	0
Bronchospasm	1 (1.4%)	0	1 (1.4%)	0
Haemoptysis	1 (1.4%)	0	1 (1.4%)	0
Laryngeal stenosis	1 (1.4%)	0	1 (1.4%)	0
Pleural effusion	1 (1.4%)	0	1 (1.4%)	0
Acute respiratory failure	0	1 (1.3%)	0	1 (1.3%)
Pulmonary arterial hypertension	0	0	0	1 (1.3%)
Pulmonary embolism	0	1 (1.3%)	0	1 (1.3%)
Respiratory failure	0	0	1 (1.4%)	0
Systemic sclerosis pulmonary	0	1 (1.3%)	0	1 (1.3%)
Blood and lymphatic system disorders	3 (4.2%)	1 (1.3%)	3 (4.2%)	1 (1.3%)
Anaemia	2 (2.8%)	1 (1.3%)	2 (2.8%)	1 (1.3%)

	Main treatment period[1]		Overall core period[2]	
	Randomized Macitentan	Randomized Standard of Care	Randomized Macitentan	Randomized Standard of Care
Antiphospholipid syndrome	1 (1.4%)	0	1 (1.4%)	0
Gastrointestinal disorders	3 (4.2%)	0	3 (4.2%)	0
Gastritis	2 (2.8%)	0	2 (2.8%)	0
Abdominal pain	1 (1.4%)	0	1 (1.4%)	0
General disorders and administration site conditions	3 (4.2%)	1 (1.3%)	3 (4.2%)	1 (1.3%)
Non-cardiac chest pain	2 (2.8%)	0	2 (2.8%)	0
Asthenia	1 (1.4%)	0	1 (1.4%)	0
Influenza like illness	0	1 (1.3%)	0	1 (1.3%)
Injury, poisoning and procedural complications	2 (2.8%)	1 (1.3%)	2 (2.8%)	1 (1.3%)
Concussion	1 (1.4%)	0	1 (1.4%)	0
Overdose	1 (1.4%)	0	1 (1.4%)	0
Thermal burn	0	1 (1.3%)	0	1 (1.3%)
Nervous system disorders	2 (2.8%)	1 (1.3%)	2 (2.8%)	3 (4.0%)
Headache	1 (1.4%)	0	1 (1.4%)	0
Status epilepticus	1 (1.4%)	0	1 (1.4%)	0
Brain oedema	0	0	0	1 (1.3%)
Dizziness	0	0	0	1 (1.3%)
Hypoxic-ischaemic encephalopathy	0	1 (1.3%)	0	1 (1.3%)
Renal and urinary disorders	2 (2.8%)	0	2 (2.8%)	0
Acute kidney injury	1 (1.4%)	0	1 (1.4%)	0
Urethral stenosis	1 (1.4%)	0	1 (1.4%)	0
Reproductive system and breast disorders	2 (2.8%)	1 (1.3%)	2 (2.8%)	1 (1.3%)
Heavy menstrual bleeding	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Uterine haemorrhage	1 (1.4%)	0	1 (1.4%)	0
Investigations	1 (1.4%)	2 (2.7%)	1 (1.4%)	2 (2.7%)
Alanine aminotransferase increased	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Oxygen saturation decreased	0	1 (1.3%)	0	1 (1.3%)
Musculoskeletal and connective tissue disorders	1 (1.4%)	1 (1.3%)	1 (1.4%)	1 (1.3%)
Costochondritis	1 (1.4%)	0	1 (1.4%)	0
Camptodactyly acquired	0	1 (1.3%)	0	1 (1.3%)
Systemic scleroderma	0	0	0	1 (1.3%)
Psychiatric disorders	1 (1.4%)	0	1 (1.4%)	0
Depression	1 (1.4%)	0	1 (1.4%)	0
Skin and subcutaneous tissue disorders	1 (1.4%)	0	1 (1.4%)	1 (1.3%)
Dermatomyositis	1 (1.4%)	0	1 (1.4%)	0
Rash	0	0	0	1 (1.3%)
Urticaria	0	0	0	1 (1.3%)
Surgical and medical procedures	1 (1.4%)	0	1 (1.4%)	0
Hospitalisation	1 (1.4%)	0	1 (1.4%)	0
Vascular disorders	1 (1.4%)	2 (2.7%)	1 (1.4%)	2 (2.7%)

	Main treatment period[1]		Overall core period[2]	
	Randomized Macitentan	Randomized Standard of Care	Randomized Macitentan	Randomized Standard of Care
Hypotension	1 (1.4%)	0	1 (1.4%)	0
Extremity necrosis	0	1 (1.3%)	0	1 (1.3%)
Thrombosis	0	1 (1.3%)	0	1 (1.3%)
Congenital, familial and genetic disorders	0	1 (1.3%)	0	1 (1.3%)
Atrial septal defect	0	1 (1.3%)	0	1 (1.3%)

Key: SAE = Serious adverse event; EOCP = End of core period; SoC = Standard of care.
[1] Main treatment period: from randomization up to end of randomized macitentan or SoC + 30 days (or EOCP, whichever comes first), or for crossover subjects up to start of macitentan or end of SoC + 30 days, whichever comes first.
[2] Overall core period: from randomization up to EOCP.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 26.1.
Only AEs with onset date occurring during the period under consideration are included.
[tsfae04.rtf] [jnj-67896062/ac-055-312/dbr_cco5/re_cco5/tsfae04.sas]; Cutoff Date: Up to individual EOCP date; Extraction Date: 2024-02-28 ; Production Date: 07MAR2024, 08:35

Source: Table 52 AC-055-312 CSR End of Core Period

17. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

The review division did not request clinical inspections for this application.

18. Labeling: Key Changes

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI (**Table 48**). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 48. Key Labeling Changes and Considerations

Full PI Sections[1]	**Rationale for Major Changes to Finalized PI[2] Compared to Currently Approved PI and Applicant's Draft PI)**
BOXED WARNING	No changes
1 INDICATIONS AND USAGE	No changes. The Applicant has not proposed any changes to this section based on the results of the TOMORROW Study and the review team agrees that the study results do not support changes to this section.
2 DOSAGE AND ADMINISTRATION	No changes
4 CONTRAINDICATIONS	No changes
5 WARNINGS AND PRECAUTIONS	No changes
6 ADVERSE REACTIONS	No changes
7 DRUG INTERACTIONS	No changes
8 USE IN SPECIFIC POPULATIONS	The Applicant has proposed updates to Section 8.4. Pediatric Use describing the results of the TOMORROW study. The review team has revised the section to include a more succinct description of the pediatric study results. The description notes that although the trial did not demonstrate a clinical benefit of macitentan compared with standard of care in the treatment of PAH, it cannot be ruled out that a trial with a different design would demonstrate a clinical benefit in this patient population (i.e., that the results are inconclusive).

9 DRUG ABUSE AND DEPENDENCE	No changes
10 OVERDOSAGE	No changes
12 CLINICAL PHARMACOLOGY	No changes
13 NONCLINICAL TOXICOLOGY	No changes
14 CLINICAL STUDIES	No changes
17 PATIENT COUNSELING INFORMATION	No changes
Product Quality Sections	No changes. Since the product will not be indicated for treatment of the pediatric population, the dispersible tablets will not be entered into the marketplace.

Source: Reviewer's table
1 Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
2 For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviation(s): PI, Prescribing Information

19. Postmarketing Requirements and Commitments

None.

20. Financial Disclosure

Table 49. Covered Clinical Study: TOMORROW

Was a list of clinical investigators provided:	Yes ☑	No ☐ (Request list from Applicant)
Total number of investigators identified: 344 (investigators and sub-investigators)		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): 0 Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Applicant of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 9		
Is an attachment provided with the reason:	Yes ☑	No ☐ (Request explanation from Applicant)

21. References

1. Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society [published correction appears in Circulation. 2016 Jan 26;133(4):e368]. Circulation. 2015;132(21):2037-2099. doi:10.1161/CIR.0000000000000329
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/s/

CHRISTINE E GARNETT
02/25/2025 03:03:53 PM

JA-AN LIN
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JAMES E TRAVIS
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I concur

JENNIFER J CLARK
02/25/2025 03:17:11 PM

YOO JIN MOON on behalf of CHONGWOO YU
02/25/2025 03:18:58 PM

YUN WANG
02/25/2025 05:53:44 PM

YOO JIN MOON
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HAO ZHU on behalf of JIANG LIU
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Sign on behalf of Dr. Jiang Liu

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